Iodine-123-4-Amino-3-Iodobenzylguanidine, a New Sympathoadrenal Imaging Agent: Comparison with Iodine-123 Metaiodobenzylguanidine

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Iodine-123-4-amino-3-iodobenzylguanidine ([^{123}I]AIBG), an analog of ^{123}I metaiodobenzylguanidine ([^{123}I]MIBG), has an advantage in having a more rapid and simple synthesis. This, combined with animal data that suggested a greater affinity of the new radiopharmaceutical for the autonomic innervation of the myocardium led us to study the biodistribution of [^{123}I]AIBG in three men with metastatic pheochromocytoma. In all instances, [^{123}I]AIBG revealed the same metastatic deposits shown by [^{123}I]MIBG. Iodine-123 AIBG uptake, however, was greater than [^{123}I]MIBG in lung, gut, and spleen. These higher backgrounds may pose diagnostic problems in some cases.

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The radiopharmaceutical, iodine-123-4-amino-3-iodobenzylguanidine nitrate ([^{123}I]AIBG) (Fig. 1), is an analog of the efficacious adrenal imaging agent metaiodobenzylguanidine ([^{123}I]MIBG and [^{131}I]MIBG) (*1*, *2*). Studies in experimental animals have demonstrated selective localization of [^{123}I]AIBG in organs rich with adrenergic innervation, such as the adrenal medulla and heart (*3*). The mechanism of concentration of AIBG appears to be the same as that for MIBG—uptake by an amine pump system and incorporation into storage vesicles (*4*). In experimental animals, AIBG has also shown greater affinity for myocardial adrenergic neurons than has MIBG (*3,5*). These characteristics of AIBG, as well as its simplified synthesis, led us to evaluate its suitability as an imaging agent for pheochromocytoma.

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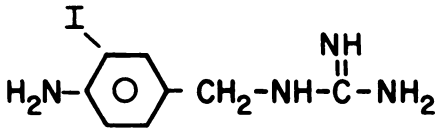
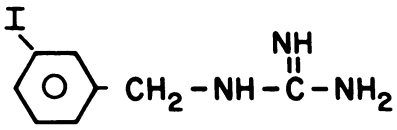
MATERIALS AND METHODS

Three men 36–48 yr of age with metastatic pheochromocytoma (documented by elevated serum norepinephrine levels, [^{131}I]MIBG scintigraphy and histologic examination) were the subjects of the investigation. Each of the patients received [^{123}I]MIBG for comparison 1 wk following the study with [^{123}I]AIBG. Patients 1 and 2 had previously received therapeutic doses (~200 mCi) of [^{131}I]MIBG.

The noniodinated precursor of AIBG—4-aminobenzylguanidine—was produced by hydrogenation of 4-nitrobenzylguanidine. Radioiodination of 4-aminobenzylguanidine by either the chloramine-T or iodogen bead method at room temperature formed [^{123}I]-4-amino-3-iodobenzylguanidine. 4.8–5.8 mCi [^{123}I]AIBG (specific activity 29.4 and 65.6 mCi/mg) was delivered intravenously over 5 min in 4–10 ml normal saline. Images were collected for 15–20 min 2.5–4.5, 21–24, and 42 hr following the infusion using a wide field-of-view gamma camera with a low-energy, parallel hole collimator. Anterior and posterior head, chest, and abdomen views provided overlapping images from the



3-iodo-4-aminobenzylguanidine (AIBG)



meta-iodobenzylguanidine (MIBG)

FIGURE 1
Structures of [^{123}I]AIBG and [^{123}I]MIBG

base of the skull to the pelvis. All data were recorded onto a dedicated nuclear medicine minicomputer for display, video formatting, and quantitative analysis. Each patient subsequently received 5.1–5.5 mCi [^{123}I] MIBG (specific activity 11.4–13.2 mCi/mg) in 1–2 ml normal saline administered by slow i.v. injection. Iodine-123 AIBG scans were compared with the [^{123}I] MIBG images, [^{131}I]MIBG diagnostic and post-therapy scintiscans (third postinfusion day). Thyroidal uptake of ^{123}I was inhibited by expansion of the inorganic iodide pool with three drops of saturated solution of potassium iodide daily (120 mg) beginning the day prior to tracer injection and continuing for 2–3 days.

Seven-milliliter blood samples were collected into ethylenetriaminetetraacetic acid containing vacutainers at 2, 5, 15, 30, and 45 min and 1, 1.5, 2, 3, 24, and 48 hr following injection of [^{123}I]AIBG, of which a portion was immediately centrifuged at 2,000 *g* for 5 min to separate the plasma. Plasma and whole-blood radioactivity was determined by counting in duplicate 0.5-ml aliquots in a standard auto-gamma scintillation spectrometer for 5 min. The radioactivity measured was corrected for decay from the time of injection and its distribution in the cellular and plasma compartments evaluated.

RESULTS

Foci of pheochromocytoma were well visualized by 2.5–4.5 hr after injection of [^{123}I]AIBG (Fig. 2). Con-

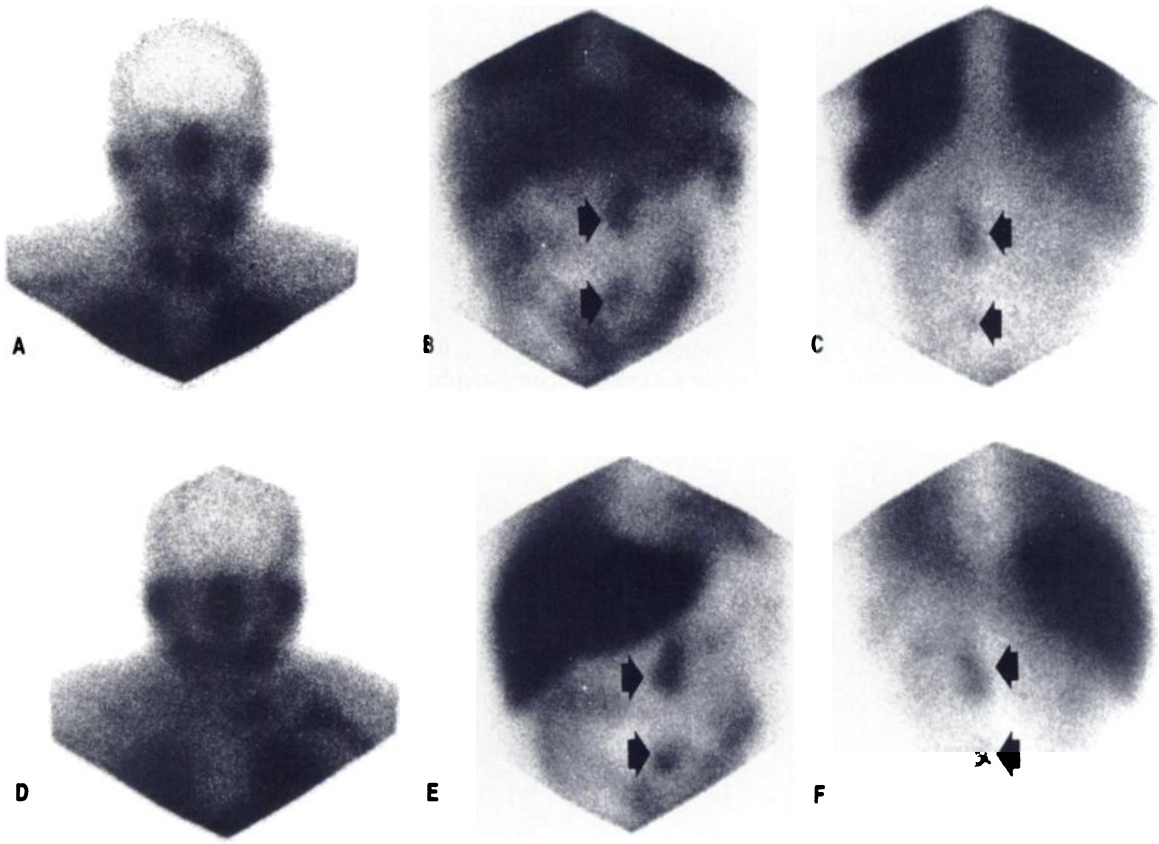


FIGURE 2
Images of Patient 1 acquired 2.5 hr following administration of [^{123}I]AIBG (top row) and [^{123}I]MIBG (bottom row). A and D: anterior head. B and E: Anterior abdomen. C and F: Posterior abdomen. Arrows depict sites of pheochromocytoma. Also noted are accumulation in salivary glands, nasopharynx, thyroid, spleen, and gastrointestinal tract

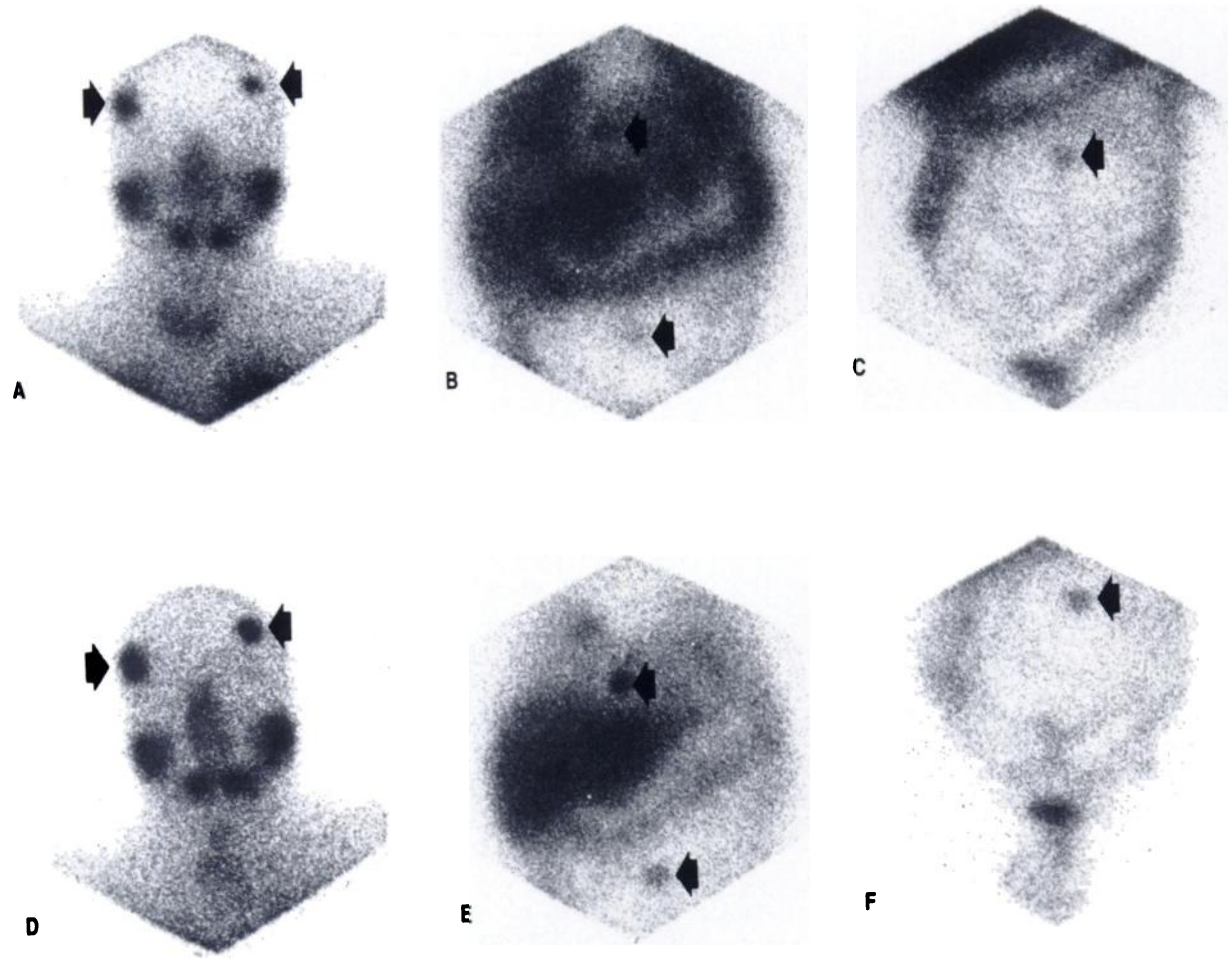


FIGURE 3
Scintigrams of Patient 2 acquired 17.5 hr following administration of [^{123}I]AIBG (top row) and 20 hr following [^{123}I]MIBG administration (bottom row). A and D: Anterior head. B and E: Anterior chest-abdomen. C and F: Anterior pelvis. Arrows depict sites of pheochromocytoma. Greater thyroidal (A), pulmonary (B), and gastrointestinal accumulation (C) are evident from [^{123}I]AIBG

centration of the radiotracer was qualitatively and quantitatively similar to [^{123}I]MIBG. All areas of abnormal accumulation demonstrated on [^{123}I]MIBG scintigraphy were identified by [^{123}I]AIBG. Delayed images showed a relative decline in background radioactivity.

Iodine-123 AIBG accumulated in many normal tissues. As with MIBG (*7*), salivary gland, nasopharyngeal, and hepatic activity were prominent (Figs. 2 and 3). Slightly greater thyroidal visualization was consistently observed. Myocardial uptake of [^{123}I]AIBG was slightly higher than that of [^{123}I]MIBG, confirming the results

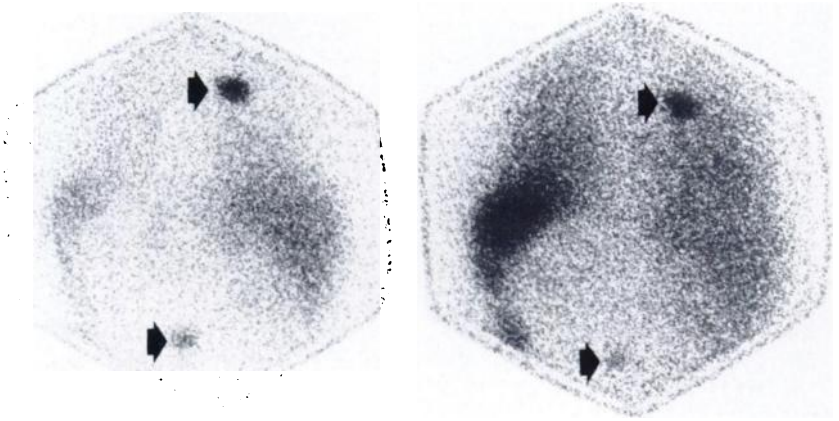


FIGURE 4
Scintigrams of Patient 2 acquired 42 hr after [^{123}I]MIBG (left) and [^{123}I] AIBG (right) of posterior chest. Abnormal foci noted by arrows. Greater splenic and pulmonary activity are noted in images obtained with [^{123}I] AIBG

TABLE 1A
[^{123}I]AIBG Biodistribution and Elimination in Three Patients (Mean ± s.e.m.)

	Time following injection			
	2 min	2 hr	12 hr	24 hr
Blood conc. (nCi/ml)	125.5 ± 10.3	54.6 ± 7.0	53.5* ± 8.5	53.4* ± 3.7
% Circulating [^{123}I] AIBG				
Plasma	57.0 ± 8.3	35.6 ± 1.3	—	18.0 ± 2.5*
Cellular compartment	43.0 ± 8.3	64.6 ± 1.3	—	82.0 ± 2.5*
Cumulative urinary excretion (%)	—	—	52.7 ± 2.0	65.1 ± 3.0
Fecal excretion (%)	—	—	—	<1.3%*

*Data available on two subjects only.

TABLE 1B
[^{123}I]MIGB Biodistribution and Elimination in Three Patients (Mean ± s.e.m.)

	Time following injection			
	2 min	2 hr	12 hr	24 hr
Blood conc. (nCi/ml)	282.2 ± 240.6 (n = 2)*	14.5 ± 1.2 (n = 3)	—	6.1 (n = 1)
			—	6.1 (n = 1)
% Circulating [^{123}I]MIBG	46.6 ± 25.7	28.0 ± 2.8	—	20.5 (n = 1)
Plasma	(n = 2)	(n = 3)		
Cellular compartment	53.4 ± 25.7 (n = 2)	72.0 ± 2.8 (n = 3)	—	79.5 (n = 1)
Cumulative urinary excretion (%)	—	—	50.0 ± 2.8 (n = 2)	64.6 ± 1.9 (n = 2)
Fecal excretion (%)	—	—	—	0.11 (n = 1)

*n = Number of subjects.

observed in experimental animals. However, pulmonary radioactivity was approximately threefold greater with [^{123}I]AIBG (Figs. 2, 3, and 4). Higher gastrointestinal and splenic uptake were also evident (Figs. 3 and 4). No side effects were observed, and no changes in cardiac rhythm or vital signs were found in any of the subjects.

Iodine-123 AIBG was eliminated by renal excretion (Table 1). Sixty to seventy percent of the administered dose was excreted in the first 24 hr, and 75–77% by 48 hr. Fecal contribution to [^{123}I]AIBG excretion was quite small. Blood radioactivity following [^{123}I]AIBG was three- to fourfold higher than following [^{123}I]MIBG and the difference remained as late as 48 hr after injection when the final samples were obtained (Fig. 5). The majority of [^{123}I]AIBG was transported within the red cells and the cellular proportion of circulating [^{123}I] AIBG rose progressively during the study, which kept the blood concentration nearly constant from 2 to 24 hr.

DISCUSSION

Iodine-123 AIBG provides scintigraphic images of abnormal adrenomedullary tissue similar to those obtained from [^{123}I]MIBG (*8*). Advantages of [^{123}I]AIBG include its electron donating amino group in the 4-position of the benzylguanidine which allows direct electrophilic substitution of radioiodine in a rapid, high yield reaction and requires <15 min at room temperature. Simplified synthesis might permit local production of [^{123}I]AIBG. In contrast, production of [^{123}I]MIBG requires a more difficult and time-consuming exchange reaction under high temperature for 1.5–2.0 hr (*3,9*).

Myocardial uptake of [^{123}I]AIBG was slightly greater than [^{123}I]MIBG. Data from experimental animals indicated that [^{123}I]AIBG might be useful in further investigating the adrenergic innervation of the heart (*3*). However, in man, the accentuated pulmonary accumulation limits the effectiveness of [^{123}I]AIBG in myocardial scintigraphy. The greater pulmonary and splenic activity appear to reflect the greater affinity of these organs for the amino-substituted compound. Localization of [^{123}I]AIBG within the spleen and gut may occasionally obscure abnormal foci of radiotracer accumulation, necessitating serial images. Since the fecal excretion of [^{123}I]AIBG, like that of [^{131}I]MIBG and [^{123}I]MIBG, is quite low, gastrointestinal visualization is likely due at least in part to concentration within adrenergic neurons at the bowel wall rather than in the luminal contents. Secretion through the bile or directly by the gut remain other possibilities.

Thus, [^{123}I]AIBG can provide scintigraphic location

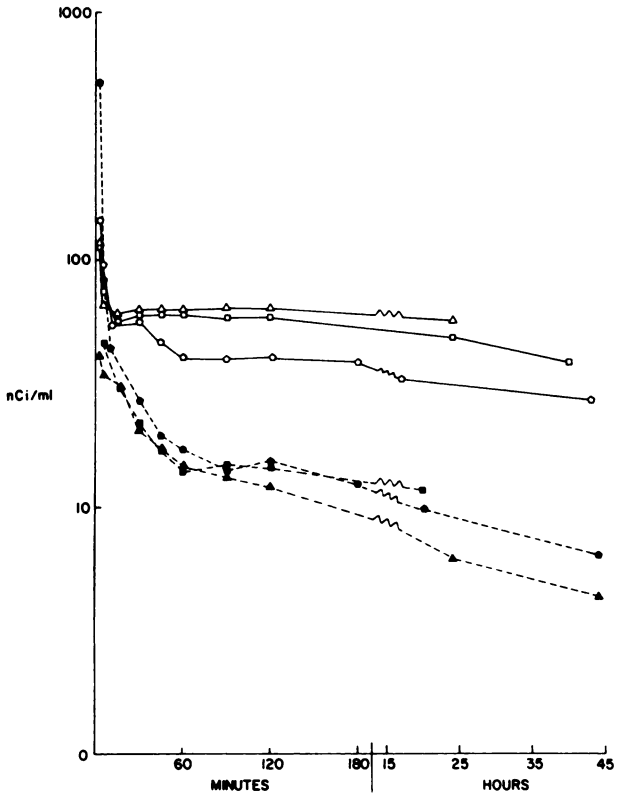


FIGURE 5
Blood clearance curves of [^{123}I]AIBG (open symbols) and [^{123}I]MIBG (closed symbols)

of pheochromocytoma similar to that obtained with [^{123}I]MIBG. However, its synthetic advantages and higher myocardial concentration are somewhat offset by its greater accumulation in normal pulmonary, splenic, and gastrointestinal areas.

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REFERENCES

1. Sisson JC, Frager MS, Valk TW, et al: Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305:12–17, 1981
2. Shapiro B, Copp JE, Sisson JC, et al: Iodine-131 metaiodobenzylguanidine for the locating of suspected pheochromocytoma. Experience in 400 cases. *J Nucl Med* 26:576–585, 1985
3. Lee H, Inbasekaran MN, Wieland DM, et al: Development of a kit-form analog of metaiodobenzylguanidine. *J Nucl Med* 27:256–267, 1986
4. Tobes MC, Jaques S, Wieland DM, et al: Effect of uptake-one inhibitors on the uptake of norepinephrine and *meta*-iodobenzylguanidine. *J Nucl Med* 26:897–907, 1985
5. Kline RC, Swanson DP, Wieland DM, et al: Myocardial imaging in man with I-123 metaiodobenzylguanidine. *J Nucl Med* 22:129–132, 1981
6. Sisson JC, Shapiro B, Beierwaltes WH, et al: Radiopharmaceutical treatment of malignant pheochromocytoma. *J Nucl Med* 24:197–206, 1984
7. Nakajo M, Shapiro B, Copp JE, et al: The normal and abnormal distribution of the adrenomedullary imaging agent m-[I-131]iodobenzylguanidine (I-131-MIBG) in man: Evaluation by scintigraphy. *J Nucl Med* 24:672–682, 1983
8. Lynn MD, Shapiro B, Sisson JC, et al: Portrayal of pheochromocytoma and normal human adrenal medulla by m-[I-123]iodomethylguanidine: Concise communication. *J Nucl Med* 25:436–440, 1984
9. Mangner TJ, Anderson-Davis H, Wieland DM, et al: Synthesis of I-131 and I-123-metaiodobenzylguanidine (MIBG) in the diagnosis and treatment of pheochromocytoma. *J Nucl Med* 24: P118, 1983 (abstr)