Metabolism of Iodine-131 Metaiodobenzylguanidine in Patients with Metastatic Pheochromocytoma

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Iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) is used to image and treat human pheochromocytoma. As part of a pharmacodynamic study of this agent, we have evaluated its excretion and metabolism in nine pheochromocytoma patients undergoing MIGB therapy. Following diagnostic doses of [^{131}I]MIBG given prior to therapy, 40 to 55% of the administered radioactivity generally appeared in the urine within 24 hr and 70 to 90% was recovered within 4 days. Reverse-phase high performance liquid chromatography was used to identify radioactive metabolites following therapeutic doses of [^{131}I]MIBG. Unaltered [^{131}I]MIBG was the major radioactive urinary component found, representing 75 to 90% of the total in all but one of the nine patients examined. The urine samples from the patient, whose rate of urinary excretion was the lowest of the group, contained [^{131}I]-*m*-iodohippuric acid ([^{131}I]MIHA) in amounts equal to that of [^{131}I]MIBG, as well as small amounts of [^{131}I]iodide and [^{131}I]-*m*-iodobenzoic acid ([^{131}I]MIBA). Iodine-131 MIHA and [^{131}I]iodide were also minor components in the urine samples from the other eight patients. Trace quantities of [^{131}I]MIBA and ^{131}I-4-hydroxy-3-iodobenzylguanidine ([^{131}I]HIBG) were also detected in a few of the patient urine samples examined. The 4- to 5-day metabolism profiles varied from patient to patient but were similar for the same patient following therapy doses given 4 mo apart. There was no obvious correlation between the presence of metabolites and the location of the tumors or the plasma or urinary catecholamine levels. Extraction of radioactivity from two pheochromocytomas removed from patients was determined to be primarily MIBG. These studies suggest that [^{131}I]MIBG is a rapidly excreted, relatively stable radiopharmaceutical agent.

J Nucl Med 27:37–44, 1986

Metaiodobenzylguanidine (MIBG), when labeled with the gamma-emitting radionuclides iodine-131 (^{131}I) or iodine-123 (^{123}I), images of pheochromocytoma (*1–5*), neuroblastoma (*6,7*), hyperfunctioning adrenal medullae (*4*), organs with rich adrenergic innervation such as the heart (*8–10*), and, with sufficiently high doses, normal adrenal medullae (*1,5,11*). In addition, the high selective affinity of [^{131}I]MIBG for pheochromocytomas has led to its use in radiotherapy (*11*).

MIBG is thought to share the same mode of uptake and retention as norepinephrine in peripheral adrenergic nerves (*8*). However, since MIBG is not a catecholamine, it would not be expected to be a substrate for the metabolic enzymes monoamine oxidase (*12*) or catechol-*O*-methyltransferase (*13*). However, guanidines structurally similar to MIBG, such as the antihypertensive drugs bethanidine (*14*), guanoxan (*15*), and debrisoquin (*16*) are metabolized to varying extents in man with the major metabolite generally being a ring hydroxylated product (*17*). Earlier studies in our laboratory suggest that MIBG is not extensively deiodinated in dogs (*18*). Currently no detailed study has been published on the metabolic fate of MIBG in either animal or man. Our interest in the metabolism of

Revision received July 23, 1985; accepted Aug. 22, 1985.

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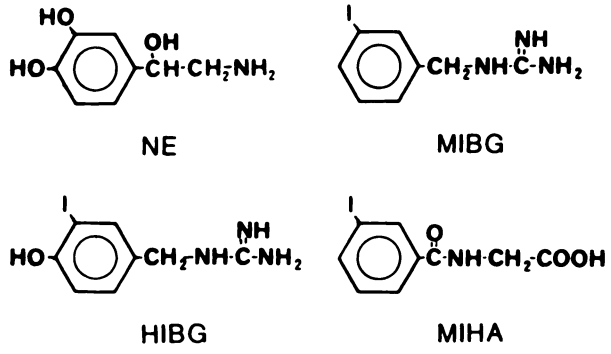

FIGURE 1
Structures of norepinephrine (NE), MIBG, HIBG, and MIHA

MIBG was kindled by our recent finding that a polar derivative of MIBG, 4-hydroxy-3-iodobenzylguanidine (HIBG) (Fig. 1), shows high accumulation in the dog adrenal medulla (*19*). This suggested the possibility that HIBG or a similar metabolite might be the active agent in human MIBG scintigraphy. Although radioactivity selectively accumulates in human pheochromocytomas following i.v. MIBG injection, the accumulation of radioactivity in these tumors generally represents < 2% of the injected dose (*3*). It is therefore tenable that even a minor metabolite of MIBG could be responsible for, or at least contributing to, the imaging of catecholamine containing tumors. The metabolic study of MIBG reported here was designed to probe this possibility. In addition, an assessment of the possible metabolism of MIBG in humans is necessary to our ongoing evaluation of MIBG as a mapping agent of the sympathoadrenal system, particularly in the development of a tracer kinetic model for use with single photon emission tomography.

We report here a radio-HPLC study of pheochromocytoma patients undergoing [^{131}I]MIGB therapy in which six radioactive metabolites were detected, including minute amounts of HIBG. However, with the exception of one patient, MIBG was not appreciably metabolized. Evidence is presented which suggests that [^{131}I]MIBG is solely responsible for the imaging of pheochromocytomas.

MATERIALS AND METHODS

Synthesis of [^{131}I]MIBG and Probable Metabolites

Iodine-131 MIBG for diagnostic use (specific activity of 0.5 to 2.0 Ci/mmol) and for therapeutic use (specific activity of 8 to 13 Ci/mmol) was prepared as previously described (*20*). Iodine-131 NaI,* *m*-iodobenzoic acid (MIBA)† and *m*-iodobenzylamine hydrochloride† were obtained from commercial sources. *m*-Iodohippuric acid (MIHA) was synthesized according to Elias et al. (*21*). HIBG was prepared by way of iodination of 4-hydroxybenzylguanidine with iodine (*19*). Iodine-131 HIBG was prepared by radioiodination of 4-hydroxybenzylguanidine in the presence of chloramine-T (*19*).

Patient Population, Diagnostic and Therapy Doses, and Collection of Urine and Tumor Tissue for Analysis

Nine patients with metastatic pheochromocytomas were studied for [^{131}I]MIBG excretion and metabolism. Their plasma and urinary hormone levels were sufficiently high to be diagnostic of pheochromocytoma. Liver function (bilirubin, alkaline phosphatase) and kidney function (urea nitrogen, creatinine) blood tests were taken within 2 wk prior to therapeutic [^{131}I]MIBG. Tumor localization was determined by scintigraphy and computed tomography as previously described (*1–5*). Diagnostic doses (0.42 to 0.53 mCi) of [^{131}I]MIBG were administered, generally, one week prior to [^{131}I]MIBG therapy. Following a diagnostic dose, successive 24-hr urine collections were analyzed for total radioactivity excreted and corrected for decay from time of dosing. Therapeutic doses (111 to 213 mCi) of [^{131}I]MIBG were administered and repeated up to four times with intervals of a minimum of 4 mo between doses. To minimize the potential hazards of handling large volumes of highly radioactive urine, 10 to 20 ml aliquots of spot urine samples were collected at 4 hr and every 24 hr for 6 days following a therapeutic dose. These were prepared for high performance liquid chromatography (HPLC) radio-analysis to identify any potential metabolites. All patients received oral potassium iodide beginning one day prior to a diagnostic dose and ending four weeks after a therapeutic dose of [^{131}I]MIBG.

Two additional pheochromocytoma patients received a diagnostic dose (0.5 mCi) of [^{131}I]MIBG prior to surgical resection of their tumors. From Patient A, a histologically-confirmed, left intra-adrenal pheochromocytoma (120 g, 7.0 × 8.5 × 2.6 cm) was resected 46 hr after [^{131}I]MIBG administration. From Patient B, a left intra-adrenal pheochromocytoma (14 g, 3.5 × 2.5 × 2.0 cm) and two right intra-adrenal pheochromocytomas (9 g, 2.5 × 1.6 × 2.0 cm; 0.26 g, 0.8 × 1.0 × 0.4 cm) were resected 65 hr after receiving [^{131}I]MIBG. Within 2 to 3 hr after surgery, the radioactivity was extracted from the tumor tissue and analyzed by radio-HPLC.

Preparation of Urine Samples: SEP-PAK Method

Each patient urine sample (3 ml), containing 5 to 100 μCi/ml of radioactivity was applied to a C-18 SEP-PAK cartridge‡ previously washed with 5 ml of methanol followed by 10 ml of 10 m*M* KI in glass distilled water. Three fractions were obtained by elution of the SEP-PAK cartridge. Fraction 1 consisted of the initial

3 ml of urine plus 5 ml of 10 m*M* KI solution passed through the cartridge. Fraction 2 (8 ml) and 3 (5 ml) were obtained by elution of either a) 0.2*M* ammonium phosphate (pH 4.6)/THF, 80/20, or b) 0.2*M* ammonium phosphate (pH 7.0)/THF, 80/20, or c) 0.2*M* ammonium phosphate (pH 7.0)/THF, 70/30.

Each of the eluted fractions and the remaining SEP-PAK cartridge was assayed for radioactivity using either a radioisotope dose calibrator[§] or an autogamma counter[¶]. In all cases, of the applied activity, Fraction 1 contained 1 to 7%, Fraction 2 contained > 93%, and Fraction 3 and the remaining SEP-PAK cartridge each contained < 1%.

Extraction and Preparation of Tumor Tissue

A 25-g portion of the pheochromocytoma resected from Patient A (containing 3.1 μCi of activity) was minced into 2 × 2 mm pieces and homogenized in 4 ml/g of 5 m*M* ammonium phosphate, pH 7.0, for 1 min at 4° C. Acetonitrile (5 ml/g of tissue) was then added and the mixture was thoroughly blended for 1 min at 4° C. The resulting suspension was centrifuged at 20,000*g* for 20 min at 10° C and the supernatant was collected and assayed for radioactivity. The recovery of the sample radioactivity into the extract supernatant was 94.1%. Similarly treated were portions of the resected tumors (11.35 g, consisting of ~ ½ of each of the three tumors and containing a total of 1.2 μCi of activity) from Patient B. Recovery in this case was 97.2%.

A 50-ml aliquot of the extract supernatant from Patient A or B was concentrated in vacuo at room temperature to 3.5 ml with the aid of a benzene azeotrope. Loss of activity in each case was < 2%. The concentrated extract (3 ml) was then applied to a C-18 SEP-PAK cartridge and eluted with 4 ml of 0.2*M* ammonium phosphate (pH 7.0)/THF, 70/30. In each case, > 97% of the activity applied to the SEP-PAK was recovered. Overall, 91.8 and 95.1%, respectively, of the radioactivity contained in the tumor samples of Patients A and B, was recovered for radio-HPLC analysis.

HPLC Analysis of [^{131}I]MIBG Metabolites

The HPLC system[**] was coupled to an ultraviolet detector (254 nm) and an integrating radiometric detector[††] which was equipped with a 200 μl solid scintillant cell for continuous monitoring of eluant radioactivity. Two μBondapak C-18 columns[‡] (4.6 × 250 mm) connected in series and equipped with a C-18 precolumn cartridge[‡‡] were utilized. Two solvent systems were employed for metabolite analyses: 0.2*M* ammonium phosphate (pH 4.6)/THF, 80/20, and/or 0.2*M* ammonium phosphate (pH 7.0)/THF, 80/20. Additionally, a solvent system of 0.2*M* ammonium phosphate at pH 7.0 (no THF) was used to confirm the presence or absence of [^{131}I]iodide in a particular sample. The flow rate was 1.5 ml/min; all analyses were done at ambient temperature.

For HPLC analysis, SEP-PAK-prepared solutions were diluted, if necessary, to a concentration of 2 to 3 μCi/ml with the appropriate elution solvent, and an aqueous solution of 10 m*M* of unlabeled MIBG and 10 m*M* NaI was added to give a final concentration of 1.0 m*M* of each. With concurrent ultraviolet and radioactive detection, the added MIBG and NaI acted as internal standards to control for slight shifts in retention times brought on by slight variations in batch to batch solvent composition and ambient temperature. Authentic unlabeled and/or labeled compounds were added to SEP-PAK prepared sample solutions for co-chromatography studies; unlabeled compounds were added to a concentration of 0.5 to 1.0 m*M* and labeled compounds ([^{131}I]NaI, [^{131}I]MIBG, [^{131}I]HIBG) to an amount of radioactivity equal to 10 to 20% of the total in the sample. Analysis of each sample was done at least in triplicate and the results were averaged. All retention times (t_R) and percent radioactivity of different peaks for a particular sample were ± 5% of the average.

RESULTS AND DISCUSSION

Major Route of Excretion of [^{131}I]MIBG and Metabolites

As shown in Fig. 2, the major route of excretion of radioactivity following diagnostic doses of [^{131}I]MIBG is by the urine. In a separate patient population, <1% of the administered diagnostic dose was detected in feces collected over a 4-day postinjection period (unpublished data). The rate of urinary excretion of radioactivity was similar for Patients 1 to 6, but was slightly lower for Patient 7, significantly lower for Patient 8 and lower still for Patient 9. The excretion kinetics were similar in the same patient following up to four separate doses of [^{131}I]MIBG that were administered 4 mo apart. The differences in the excretion kinetics of Patients 7, 8 and 9 could not be explained on the basis of the administered dose in terms of activity or specific activity. The reduced rate of excretion for Patients 7, 8, and 9 may be related to the functional state of their kidneys since their blood urea nitrogen and serum creatinine levels were marginally elevated over established norms (*22*) (BUN and creatinine values were, respectively, for Patient 7, 23.7 mg/dl and 1.5 mg/dl; for Patient 8, 25.4 and 1.1; and for Patient 9, 27, and 1.2). These values remained elevated for Patients 7 and 8 over the 2-yr period in which they were examined. The rate of urinary excretion of radioactivity from Patients 1 to 6 closely paralleled that reported for normal volunteers (*23*), indicating that the presence of tumors which take up and retain [^{131}I]MIBG had little effect on the rate, amount, or route of excretion.

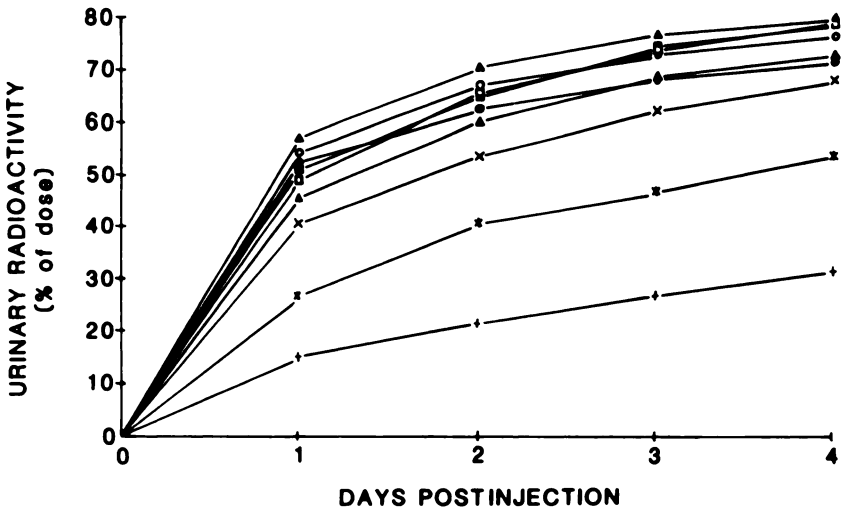

FIGURE 2
Urinary excretion of total radioactivity in pheochromocytoma patients following diagnostic [^{131}I]MIBG. (●) Patient 1 (n = 1); (O) Patient 2 (n = 2); (■) Patient 3 (n = 2); (□) Patient 4 (n = 2); (▲) Patient 5 (n = 1); (△) Patient 6 (n = 1); (x) Patient 7 (n = 4); (*) Patient 8 (n = 4); (+) Patient 9 (n = 1). (Numbers in parentheses represent number of separate doses for each patient that were examined and of which average is plotted)

The rate of urinary excretion of radioactivity following therapeutic doses of [^{131}I]MIBG appears to be similar to that following diagnostic doses. Total urinary output was collected and excretion rates beginning 3 days after administration of therapeutic doses of [^{131}I]MIBG were measured in two of the nine patients (Patients 7 and 8). For Patient 7, 6.1 to 6.8% of three separate therapeutic doses appeared in the urine from 3 to 4 days postinjection while 3.9 to 4.8% was excreted between Days 4 and 5. These values were not significantly different than the corresponding values obtained with the preceeding diagnostic doses, 5.5 to 6.4% and 4.0 to 4.5%. Similarly, the 3- to 4-day value of 6.8% and 4- to 5-day value of 5.0% following a therapeutic dose to Patient 8 compared to 6.7 and 5.7%, respectively, for the preceeding diagnostic dose. This indicates that the kinetics of elimination are relatively constant with loading doses of MIBG ranging from ~ 0.15 mg (diagnostic dose) to ~ 5 mg (therapeutic dose) and relatively independent of activity and specific activity of the administered dose.

HPLC Identification of Metabolites

The HPLC system used in this study was developed from earlier work on the synthesis of aralkylguanidines (*18,20,24*), in which its efficiency at separating a mixture of over 15 structurally similar aralkylguanidines, including ortho-, meta-, and para-iodobenzylguanidine, was demonstrated. Figure 3 shows the HPLC separation of MIBG and several iodinated compounds that would most likely result from any in vivo metabolism of MIBG. Although the retention times for MIBG, HIBG, iodide, and iodate were little affected by the pH of the elution solvent, those of the potential acidic metabolites, MIHA and MIBA, and the potential hydrolysis product, *m*-iodobenzylamine, showed substantial pH-dependent shifts in retention times which aided in their chromatographic identification.

The solvent system with no THF was used to determine presence or absence of iodide (t_R = 4.5 min). Its use revealed that the SEP-PAK procedure cleanly separates radioiodide from the other urinary MIBG metabolites; radioiodide comprised at least 90% of the activity contained in Fraction 1 (KI elution) and < 1% of the major Fraction 2 eluted from the SEP-PAK with the THF-containing buffers.

In addition to the small amounts of radioiodide, the other radioactive compounds contained in Fraction 2, as determined by co-chromatographic elution with authentic unlabeled compounds added to selected samples, are those depicted in Fig. 3, namely MIBG, MIHA, and MIBA. In no instance was *m*-iodobenzylamine or iodate detected in any of the samples examined. Also detected in all samples were two additional minor radioactive peaks with t_R's of 5 and 6 min representing, respectively, 1 to 2% and < 0.5% of the total radioactivity in the sample. These peaks likely represent more highly oxidized forms of radioiodide, such as triiodide or higher polyiodides based on the following observations: (a) the areas of the three peaks with t_R's of 4.5 (radioiodide), 5 and 6 min appeared in a fairly consistent ratio of 1:2:0.5 in the chromatograms of all the samples examined, and (b) the areas of the latter two

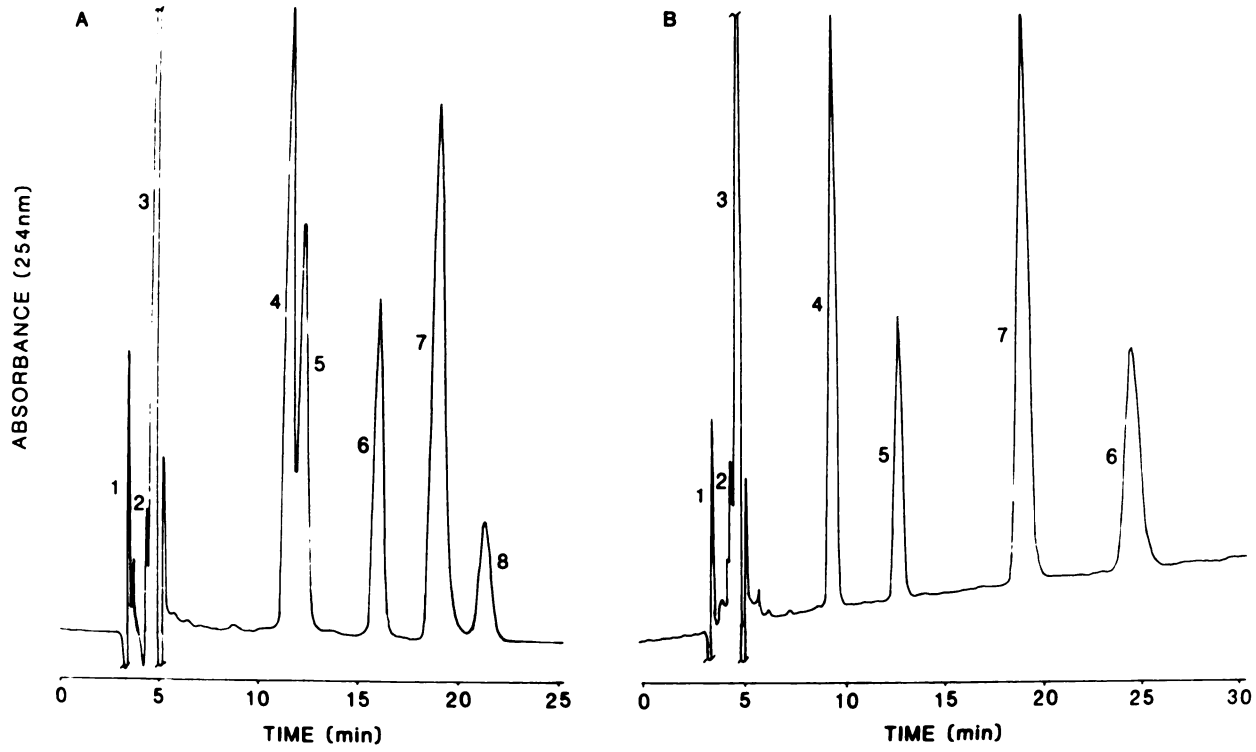

FIGURE 3
HPLC chromatograms of mixture of MIBG and its potential metabolites. Elution with (A) 0.2*M* $(NH_4)H_2PO_4$(pH 4.6)/THF, 80/20; (B) 0.2*M* $(NH_4)H_2PO_4$ (pH 7.0)/THF, 80/20. Observed peaks correspond to: (1) sodium iodate; (2) sodium iodide; (3) 4-hydroxybenzylguanidine; (4) *m*-iodobenzylamine; (5) HIBG; (6) MIHA; (7) MIBG; (8) MIBA

peaks increased at the expense of the radioiodide peak following acidification of the urine sample with acetic acid and incubation at 37° C prior to workup.

Quantitation of Metabolism

With the exception of those from Patient 9, the primary radioactive component in all the urine samples tested was identified as [^{131}I]MIBG. This was particularly true at early time intervals (4 and 24 hr postinjection) where, invariably, at least 85% of the radioactivity present was unaltered [^{131}I]MIBG. Also consistently present in all the urine samples examined were, as previously mentioned, radioiodide, representing 2 to 5% of the urinary radioactivity from Patients 1 to 7, and the two minor radioactive components associated with it. Iodine-131 HIBG and [^{131}I]MIBA were either absent or present in very small quantities (< 0.5%) in all cases except for urine samples from Patients 8 and 9 (vide post).

The primary metabolite of [^{131}I]MIBG, in addition to radioiodide, was found to be [^{131}I]MIHA, present in all the urine samples examined. However, in contrast to radioiodide, which represented a fairly constant proportion of the urinary radioactivity over the postinjection period, there was considerable variation in the urinary appearance of [^{131}I]MIHA among the patients examined. Figure 4 shows the relative composition of the daily urine samples of four of the patients examined with respect to iodide, MIHA, MIBG and MIBA following therapeutic doses of [^{131}I]MIBG. Variation in the appearance of MIHA among the patients studied is evident when the relative contribution of [^{131}I]MIHA to the daily urinary activity is examined over the 4 to 5 day postinjection period. Patients 1 and 3, as illustrated in Fig. 4 represent two distinctly different patterns of MIHA excretion dynamics that were observed: (a) the amount of MIHA relative to MIBG and other metabolites steadily increased over a 3- to 4-day period before reaching equilibrium (Patient 1), and (b) the equilibrium level of MIHA was quickly (within 1 day) attained at values generally lower than those of the increasing type (Patient 3). Of the patients examined in this study, Patients 1, 2, and 6 were of the former type and Patients 3, 4, 5, and 7 were of the latter. The similarity of the excretion profiles in the same patient following two separate doses, illustrated in Fig. 4 by Patient 3, was also observed in Patients 2 and 4 where separate doses were examined (data not shown).

In all but one patient (Patient 9), the fraction of the radioactivity present as [^{131}I]MIBG was greatest in early urine samples (up to 1 day postinjection). Since, from the excretion rate profile (Fig. 2), this also represents the time interval during which most of the administered radioactivity is excreted, the amount of

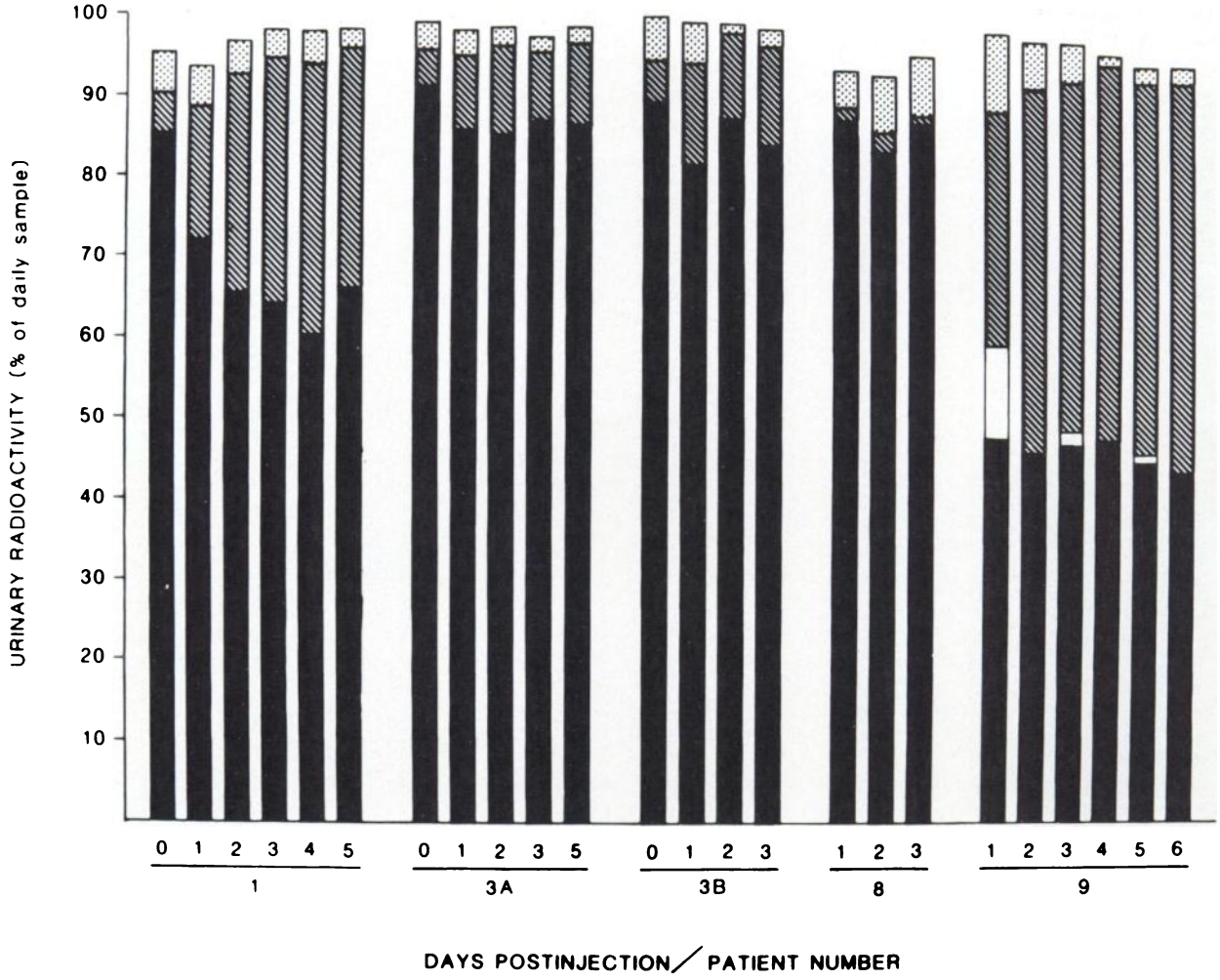

FIGURE 4
Radioactive composition of daily urine samples of pheochromocytoma patients following therapeutic [^{131}I]MIBG. Two separate doses (3a & 3B) are represented for Patient 3. (■) MIBG; (□) MIBA; (▩) MIHA; (□) Iodide

[^{131}I]MIBG contained in these early samples represents a significant portion of the total excreted radioactivity. Conversely, since increasingly less of the administered dose is contained in later urine samples, the MIHA contained in these samples, although representing a greater proportion of the radioactivity present, does not contribute as heavily to the total. Through a rough extrapolation involving both the HPLC data and excretion curve, the portion of a therapeutic dose of [^{131}I]MIBG excreted as the unaltered compound is estimated at 75 to 90% for all patients studied except for Patient 9.

The metabolism profiles of Patients 8 and 9, who exhibited reduced urinary excretion, were unique among the patients tested. As illustrated in Fig. 4, Patient 8 showed very little excretion of [^{131}I]MIHA. Additionally, Patient 8 excreted the highest amount of [^{131}I]HIBG of the patients in the test group, representing ~ 2% of the urinary radioactivity in each of the samples examined by HPLC. Perhaps related to this second characteristic were the relatively high levels of radioiodide excreted by this patient. Deiodination concurrent with metabolic hydroxylation is well described in similar iodoaromatic compounds (*25*) and would also be expected to occur during the hydroxylation of [^{131}I]MIBG. In contrast, almost half of the urinary radioactivity of Patient 9 was excreted as [^{131}I]MIHA beginning as early as 1 day following [^{131}I]MIBG administration. In addition, this patient's urine showed the only significant levels of [^{131}I]MIBA of the patients examined.

The data suggest that although MIBG is excreted largely as the unaltered compound, metabolism can increase with increased residence time. This is illustrated by the proportionately larger amount of MIHA excreted at longer time intervals (Patients 1,2,6) and in cases where increased residence time is brought on by renal impairment (Patient 9).

HPLC Identification of Tumor-Extracted Radioactivity

HPLC analysis revealed that 97 to 98% of the radioactivity extracted from Patient A's tumor was in the form of [^{131}I]MIBG, with the remaining 2 to 3% as radioiodide. From Patient B's tumors, [^{131}I]MIBG was the only radioactive compound detected. This indicates that [^{131}I]MIBG and not [^{131}I]HIBG or some other metabolite is being taken up by the tumor and, furthermore, that no metabolic alteration of [^{131}I]MIBG is taking place within the tumor.

General Comments and Conclusions

Results of the present metabolic study of [^{131}I]MIBG in pheochromocytoma patients indicate that [^{131}I]MIBG is not appreciably metabolized and is excreted by way of the kidneys primarily as the unaltered compound.

Analysis of the radioactivity extracted from pheochromocytomas following [^{131}I]MIBG administration indicates that MIBG, and not HIBG or some other metabolite, is solely responsible for the observed images in humans. Consistent with this are the following observations.

1. In vitro uptake studies with bovine adrenomedullary cells (*26*) and human pheochromocytoma cells (Jaques and Tobes, unpublished data) have shown that MIBG is avidly sequestered by the uptake carrier that transports norepinephrine.

2. Biodistribution studies of radiolabeled MIBG in dogs show that radioactivity accumulates in 5 min or less in the adrenal medullae (*2*).

3. Human pheochromocytomas are often imaged one day or less after i.v. injection of [^{131}I]MIBG (*1*).

In view of this rapid adrenal accumulation of radioactivity following [^{131}I]MIBG administration, the delayed appearance of urinary metabolites described in this paper (Fig. 4) is inconsistent with a metabolite being the active imaging agent.

FOOTNOTES

* Du Pont NEN Medical Products, Boston, MA.

† Aldrich Chemical Co., Milwaukee, WI.

‡ Waters Associates, Milford, MA.

§ Capintec, Model CRC-5R.

¶ Packard, Model 1185.

** Waters Associates, 730 System Controller; 720 Data Module; M45 and M6000 pumps; a U6K injector; 440 Ultraviolet Detector (254 nm).

†† Radiomatic, Flo-One DR radiometric detector.

‡‡ Brownlee, 3 cm RP-18 cartridge.

ACKNOWLEDGMENTS

The authors thank Ms. Shirley Mallett for providing patient samples, Mr. Lawrence Brown, Mr. Philip Sherman, and Ms. Susan Fisher for technical assistance, the Phoenix Memorial Laboratory for use of their radiochemistry facilities, Ms. Linder Markham for help in preparation of the manuscript, and Dr. William Beierwaltes for his enthusiastic support of this research.

This work was supported by N.I.H. Grant HL-27555 and by private funds.

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