Scintigraphy and Treatment of Medullary Carcinoma of the Thyroid with Iodine-131 Metaiodobenzylguanidine

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We report our experience using [^{131}I]metaiodobenzylguanidine (MIBG) to image nine patients with proven medullary carcinoma of the thyroid (MCT). Positive uptake was seen in four patients, equivocal uptake in one patient, and no uptake in four patients. Data is presented to demonstrate the pharmacokinetics of [^{131}I]MIBG in three of the patients studied. Two patients, with diarrhea and severe pain from known bone metastases and positive uptake on [^{131}I]MIBG diagnostic scanning, subsequently received therapeutic doses of [^{131}I]MIBG, with marked improvement in both pain and diarrhea, but no evidence of significant biochemical response. Iodine-131 MIBG uptake in patients with MCT is variable, and gives a higher false-negative rate than is found when using [^{131}I]MIBG to image other neuroectodermally derived tumors. The therapeutic potential of [^{131}I]MIBG in patients with MCT warrants further evaluation, in view of the symptomatic relief experienced following therapy doses in two patients with extensive disease.

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Medullary carcinoma of the thyroid (MCT) is an uncommon tumor that accounts for 2% to 9% of all thyroid malignancies. It is derived from neuroectoderm and may occur as a solitary tumor, or as part of the multiple endocrine neoplasia syndrome. Reports have demonstrated significant uptake of iodine-131 metaiodobenzylguanidine ([^{131}I]MIBG) in other neuroectodermally derived tumors, pheochromocytoma (*1*), neuroblastoma (*2,3*), and carcinoid tumors (*4*), and recently uptake of [^{131}I]MIBG has been demonstrated in patients with MCT (*5–10*). Uptake, however, has been shown to be variable, and we report our experience of imaging and therapy in patients with MCT using [^{131}I]MIBG.

PATIENTS

Nine patients were studied, one prior to surgery with primary tumor situated in the thyroid. The eight remaining patients had biochemical evidence of recurrence following surgical treatment for their primary tumor. Of the nine patients, six were female and three male, age range 24 to 74 yr (mean 48 yr). Two patients had familial disease, while the remaining seven patients were sporadic cases of MCT.

Six of the nine patients studied were symptomatic, with bone pain and diarrhea. One further patient had symptoms of bone pain alone. One patient imaged prior to surgery for the primary tumor complained of discomfort in the thyroid, and two patients were asymptomatic despite biochemical evidence of recurrence.

METHOD

The patients were imaged with 1 mCi (37 MBq) [^{131}I]MIBG injected intravenously. Whole-body scans were acquired at 24 and 48 hr after injection. Scintigrams were obtained using a large field-of-view gamma camera with a 20% window at 364 keV and a medium-energy, parallel hole collimator. Scans were also obtained 5 and 7 days following therapy injections of 100 mCi (3,700 MBq) and then 150 mCi (5,500 MBq) [^{131}I] MIBG in two patients. All patients received Lugol's iodine, ten drops daily for 24 hr preceeding and 7 days following scanning, to prevent uptake of free ^{131}I by residual normal thyroid tissue. During diagnostic scanning, three patients had blood samples taken at times 0, 5 min, and 1, 2, 3, 4, 24, 48, and 72 hr postinjection, and urine samples hourly postinjection, to study the pharmacokinetics of [^{131}I]MIBG in this group. Estimations of serum calcium, phosphate, alkaline phosphatase, aspartate transaminase and calcitonin were mon-

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TABLE 1
Results of ^{99m}Tc Bone Scan, CAT Scanning, and [^{131}I]MIBG Scanning in Patients Studied

Patient no.	Calcitonin pg/ml n = <100	[^{99m}Tc]MDP Bone scan	CAT scan	[^{131}I]MIBG scan	Assessment	[^{131}I]MIBG Rx
1	1,096	−	−	+	TP*	NP§
2	6,100	+	+	+	TP	+
3	8,970	+	+	+	TP	+
4	995	−	−	−	TN†	NP
5	2,200	+	+	+	TP	NP
6	1,200	−	+	−	FN	NP
7	5,310	+	+	+/−	E‡	NP
8	3,540	+	+	−	FN¶	NP
9	2,400	−	+	−	FN	NP

* TP = True positive.
† TN = True negative.
‡ E = Equivocal.
§ NP = Not performed.
¶ FN = False negative.

itored weekly after treatment to assess the effects of therapy on liver function and bone metabolism, as well as the response of tumour to therapy. Hemoglobin measurements, white cell and platelet counts were also performed to determine radiation effects on the marrow. Random serum cortisol measurements were made to assess adrenocortical function after therapy in view of the estimated radiation dose to the adrenals.

RESULTS

Diagnostic Imaging

The results for the nine patients were tabulated (Table 1). [^{131}I]MIBG scans were positive in four patients, Patients 1, 2, 3, and 5 (Figs. 1, and 2). Patient 1, with uptake of [^{131}I]MIBG in both lobes of the thyroid, was subsequently shown at surgery to have bilateral tumor, confirmed histologically as bilateral medullary carcinoma of the thyroid. Patients 2, 3, and 5 had known metastatic disease, and [^{131}I]MIBG identified some, but not all, known lesions in these patients. Soft-tissue metastases and bone metastases with soft-tissue extension appeared to take up [^{131}I]MIBG to a greater degree than discrete bone metastases. In one patient with known pulmonary metastases, Patient 7, equivocal uptake was seen in the lung fields. Nonspecific liver uptake was seen in the 24-hr image in all patients, but cleared by 48 hr in all patients except Patient 3, with known hepatic metastases.

The remaining four patients had no abnormal uptake seen on [^{131}I]MIBG imaging. One of these patients, despite elevated calcitonin levels, was asymptomatic and had no other evidence of recurrence, despite extensive investigation, including CAT scan and a technetium-99m methylene diphosphonate bone scan. This patient may represent a true negative scan, although elevated calcitonin levels persist. The [^{131}I]MIBG scans in the other four patients gave a false-negative result, with no uptake seen either at the sites of known bone or soft-tissue metastases (Fig. 3).

Iodine-131 MIBG Therapy

Patient 2

Diagnostic scanning in the patient revealed significant uptake in the skull, in the known deposit at the level of L2 and in the deposit in the left iliac crest. In view of the patient's marked bone pain from these lesions, and incapacitating diarrhea, it was decided to treat with a therapeutic dose 100 mCi (3,700 MBq)

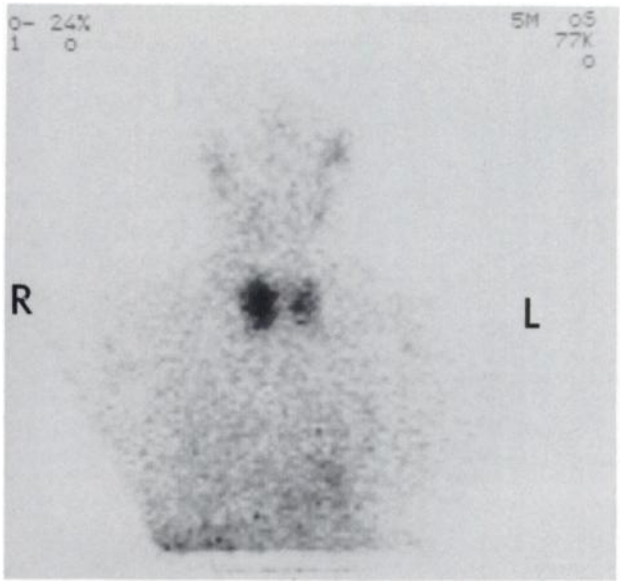

FIGURE 1
Anterior view, 24-hr diagnostic [^{131}I]MIBG scan, of Patient 1 with a known family history of MCT showing accumulation of [^{131}I]MIBG in both lobes of the thyroid, confirmed on subsequent surgery to be in sites of histologically proven MCT.

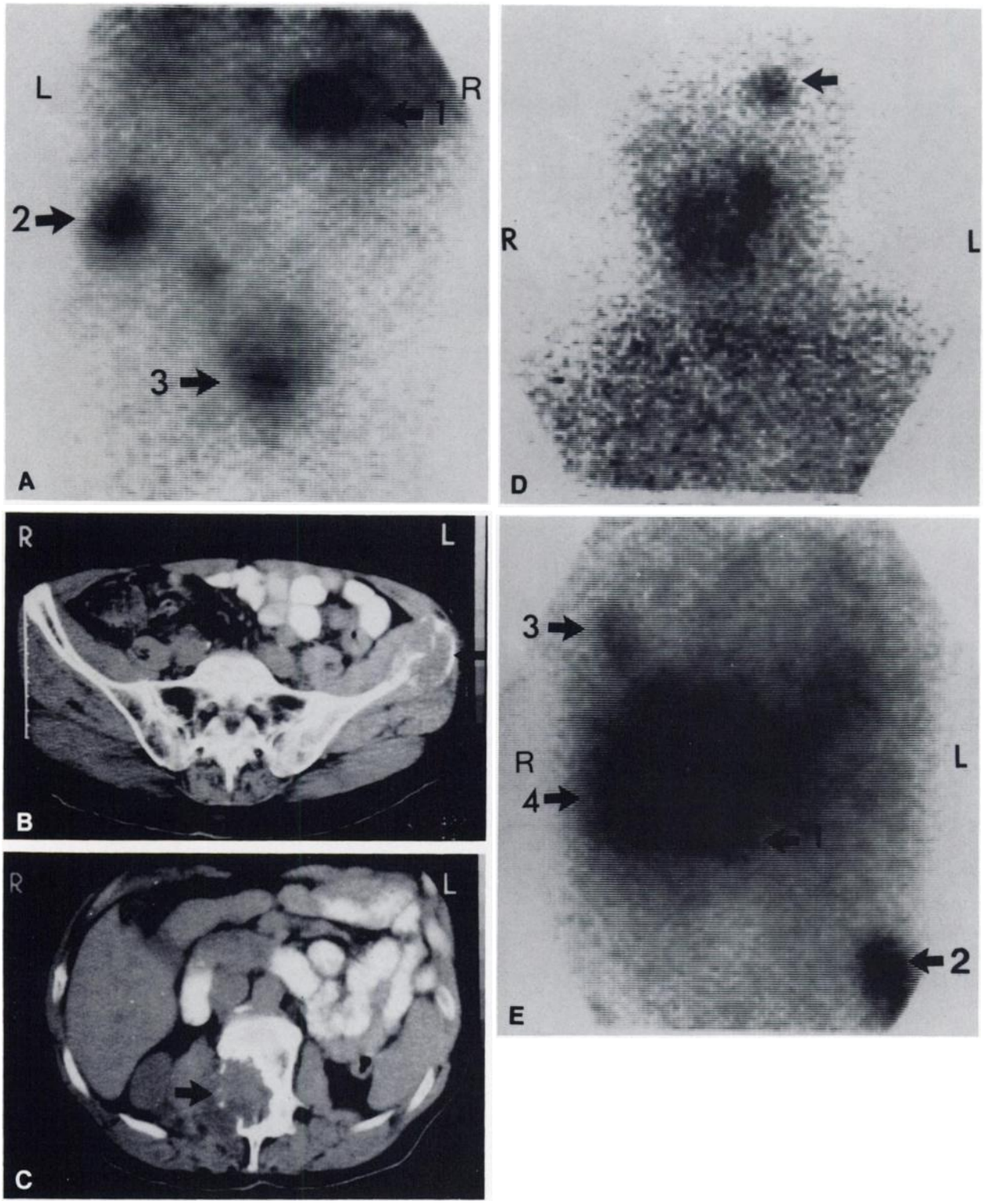

FIGURE 2
Scans of Patient 2 with known metastases in skull, lumbar spine and left iliac crest. A: 24-hr diagnostic [^{131}I]MIBG scan, posterior view, showing uptake in lumbar spine (1) and left iliac crest (2). Bladder activity is seen (3). B: CAT scan of pelvis showing tumor involving left iliac crest (arrow). C: CAT scan of L2 showing tumor destruction of body of vertebra with soft-tissue extension (arrow). D: 24 hr diagnostic [^{131}I]MIBG scan of lateral skull showing accumulation in left lateral skull metastasis. E: Six-day post-therapy [^{131}I]MIBG scan, anterior view of lower thorax and abdomen, showing good uptake in lumbar spine (1) and iliac crest (2), and identifying previously nonvisualized rib metastasis (3). Liver uptake is also seen (4) presumed to be nonspecific.

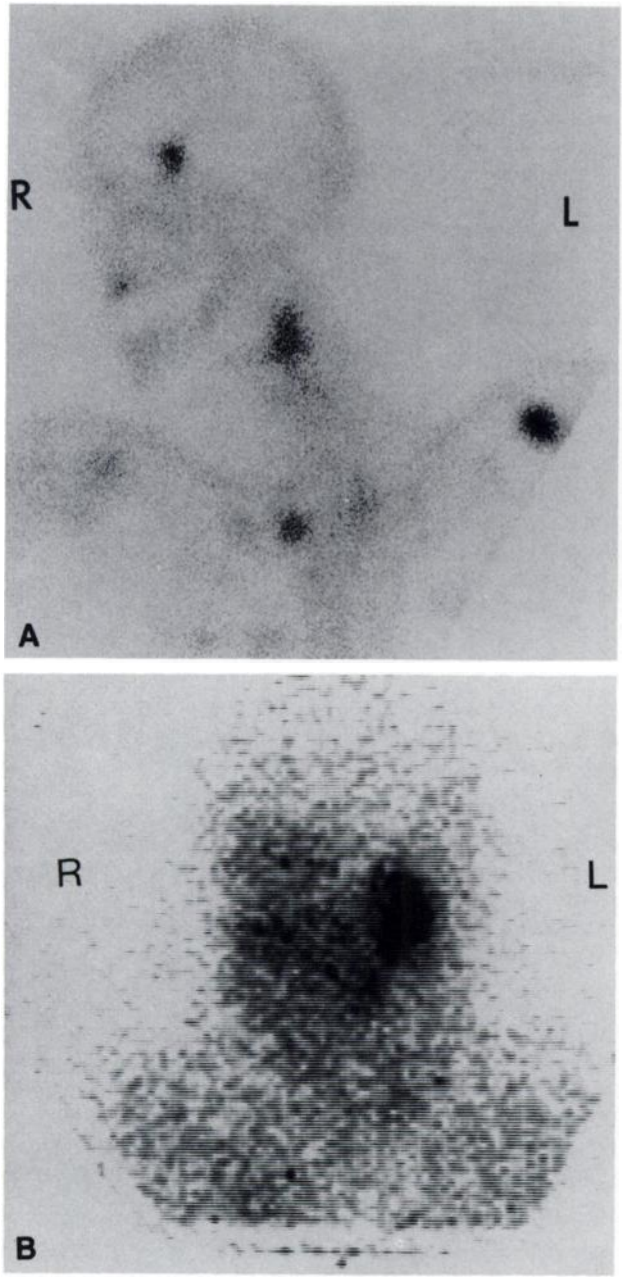

FIGURE 3
Scans of Patient 8 with widespread bony metastases from MCT. A: [^{99m}Tc]MDP bone scan of head and neck showing multiple bone metastases in skull, cervical spine, right sternoclavicular joint and left shoulder. B: [^{131}I]MIBG 24-hr diagnostic scan of head and neck showing no significant uptake in sites of known bony metastases and normal [^{131}I]MIBG uptake in left parotid gland.

[^{131}I]MIBG, after the positive diagnostic scan had been obtained. Therapy was well tolerated, with no reported or observed side-effects, and post-therapy scanning confirmed uptake of [^{131}I]MIBG in known metastatic sites and also identified a further rib metastasis, not seen on diagnostic imaging. Liver uptake was also a prominent feature on the therapy scan and was presumed to be nonspecific and dose related in view of the absence of other evidence to suggest liver metastases (Fig. 2E). Following therapy the patient experienced pain relief for a 2-mo period. A second therapeutic dose of [^{131}I] MIBG 150 mCi (5,500 MBq) was given 4 mo later. Again, the patient experienced pain relief and also improvement in diarrhea, with a short period during which antidiarrheal agents were not required, and objective reduction in the size of the soft-tissue skull deposit. However, these improvements lasted only 6 to 8 wk, and the diarrhea and the skull metastasis recurred, although the patient still believed the pain was a less marked feature than before treatment. Random cortisol levels performed after therapy showed a reduction in cortisol secretion between 4 to 8 wk following therapy. This, however, spontaneously recovered by 3 mo. The platelet count was also seen to fall transiently, with again spontaneous recovery by 3 mo after therapy. Calcitonin levels fell transiently after each therapy dose, but the fall was not sustained and 2 mo after therapy the calcitonin level started to rise again.

The calculated dose to the skull lesion was 950 cGy per 150 mCi (5,500 MBq) [^{131}I]MIBG, and to the lesion at L2 was 800 cGy per 150 mCi (5,500 MBq) [^{131}I] MIBG. The dose to the left iliac crest lesion could not be calculated due to the infiltrative nature of the lesion, which made accurate sizing impossible. The adrenal dose was calculated as 3,000 cGy to the adrenal medulla, per 150 mCi (5,500 MBq) [^{131}I]MIBG dose.

Patient 3

This patient was known to have hepatic, pleural, and rib metastases, and the hepatic metastases were identified on [^{131}I]MIBG diagnostic imaging with equivocal uptake seen in the known rib and pleural lesions. This patient was grossly symptomatic with pain from bony metastases and diarrhea, and it was again decided, therefore, to attempt therapy with 100 mCi (3,700 MBq) dose of [^{131}I]MIBG after the positive diagnostic scan. The patient experienced nausea and vomiting during the five days following the treatment dose. Pain relief was experienced for 2 mo after treatment, and a second treatment dose 150 mCi (5,500 MBq) [^{131}I] MIBG was given 3 mo later. The patient was given prochlorperazine intramuscularly prophylactically prior to administration of the second therapy dose and during the subsequent 5 days, with minimal nausea experienced. The patient again experienced pain relief, and some improvement in frequency of diarrhea following therapy but, as in Patient 2, the improvement had subsided by 8 wk post-therapy. There was no significant fall in calcitonin levels following treatment, but some increase followed by a fall in aspartate transaminase levels were noted. The estimated dose of the liver from a 150 mCi (5,500 MBq) [^{131}I]MIBG dose was 2,000 cGy.

Pharmacokinetics

The clearance of radioactivity from the blood was studied in one patient after a diagnostic study (Patient 8), and in two patients (Patients 2 and 3) after diagnostic and therapeutic doses of [^{131}I]MIBG. Urine was collected in all three patients after the diagnostic dose.

Blood clearance curves of radioactivity (Fig. 4) appeared to be triphasic. A rapid early clearance with a half-life of ~40 min occurred in all three patients, with < 10% of the dose remaining in the blood 5 min after injection. This phase was followed by a short second phase with a half-life of ~9 hr. The third phase varied between patients, being shortest in Patient 3 (half-life 47 hr), 60 hr in Patient 8, and 90 hr in Patient 2 (both diagnostic and therapeutic doses). In all cases, <1% of the dose remained in the blood at 48 hr.

Approximately 30% to 60% of the administered dose was excreted in the urine within 24 hr of injection (Fig. 5) rising to 40% to 80% at 48 hr.

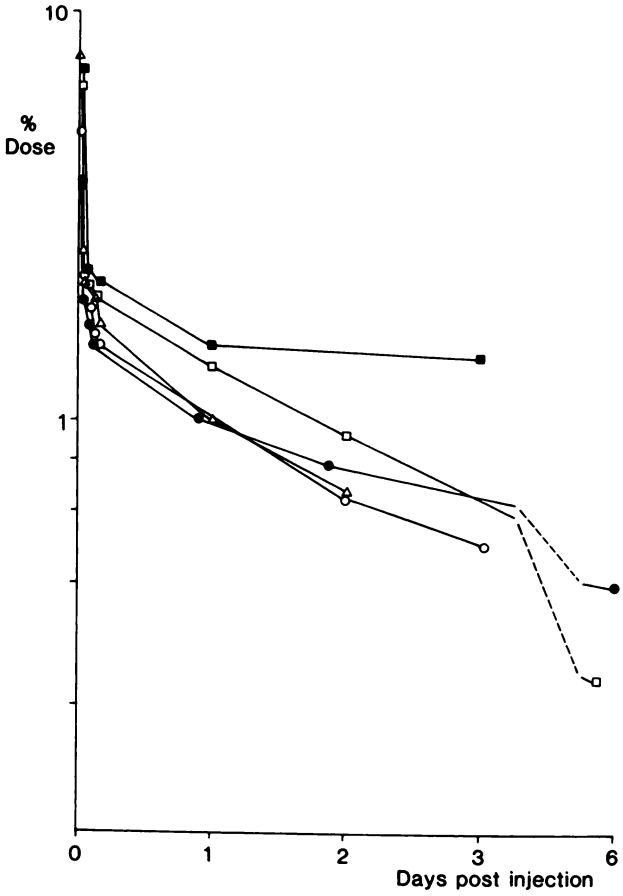

FIGURE 4
Disappearance of total radioactivity from whole blood in patients receiving diagnostic and therapeutic doses of [^{131}I] MIBG. Patient 2 (○, therapy), (●, diagnostic); Patient 3 (□, diagnostic), (■, therapy); Patient 8 (△, diagnostic).

DISCUSSION

Iodine-131 MIBG uptake in neuroectodermally derived tumor is now well described and several case reports (*5–7*) and a series of six patients (*8*) have been reported demonstrating uptake of [^{131}I]MIBG in patients with MCT. The series reported by Poston et al., however, shows that uptake is variable, and that in some patients with proven MCT recurrence, no uptake of [^{131}I]MIBG is visualized. Our series of nine patients confirms the findings of Poston et al., with equivocal uptake seen in one patient with known metastases and no uptake seen in four patients with elevated calcitonin levels, of whom one had no other evidence of metastases with normal CT and bone scan. Four patients, however, one with primary tumor and three with proven metastases, had definite [^{131}I]MIBG uptake.

The mode of [^{131}I]MIBG uptake in MCT is uncertain. In pheochromocytoma, uptake occurs in the neurosecretory granules, but no such uptake has yet been demonstrated in MCT. In this study, we have visualized uptake in known sites of MCT, but it is of interest that not all sites of known tumor in an individual patient take up [^{131}I]MIBG to the same degree. As has been demonstrated in Patient 2, soft-tissue metastases appear to take up [^{131}I]MIBG more avidly than discrete bone metastases, that may explain some of the variation in uptake seen in individual patients. Post-therapy imaging in Patients 2 and 3 also indicates that more tumor sites are identified with high doses of [^{131}I]MIBG than are seen with the 1 mCi (37 MBq) dose, a finding often observed in patients with follicular carcinoma of the thyroid, in whom the low dose diagnostic ^{131}I scan is negative, but the post high-therapy dose scan is positive.

The pharmacokinetic studies indicate that [^{131}I]MIBG in patients with MCT is excreted in a similar pattern to that reported by Mangner et al. (*11*) in patients with malignant pheochromocytoma. The lowest percentage excretion at 24 hr was seen in the patient with most uptake on the scan indicating significant retention of activity in that patient.

Iodine-131 MIBG therapy was given to two patients with widespread metastatic disease. Both patients experienced pain relief after therapy, and both also experienced a short-term improvement in diarrhea after the second treatment dose. Disappointingly, neither patient showed a sustained reduction in calcitonin level after therapy, and pain and diarrhea relief lasted only 2 mo after treatment. The estimated radiation doses to the lesions in both patients were low, which presumably explains the absence of a dramatic response to therapy. The fact that there was any response at all may be due to the kinetics of MCT, a slow-growing tumor that is possibly more likely to respond to low dose continuous radiation than an agressive tumor. However, in view of the symptomatic relief, this study would suggest that there may be a palliative role for [^{131}I]MIBG in patients

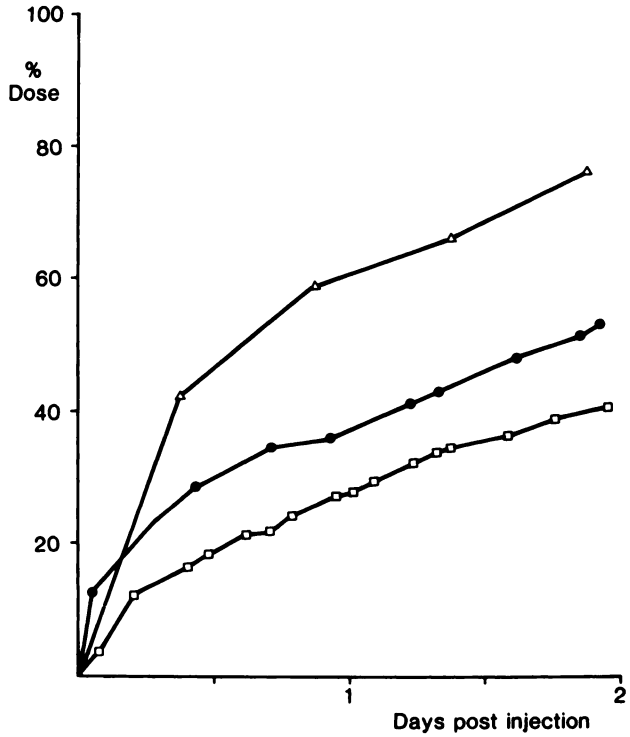

FIGURE 5
Urinary excretion of total radioactivity in patients receiving diagnostic doses of [^{131}I]MIBG. Patient 8 (Δ); Patient 2 (●); Patient 3 (□).

with MCT that take up [^{131}I]MIBG. Therapy, however, should be considered earlier in the disease, and doses given at 2-month rather than 3- to 4-month intervals, as in this study. Unfortunately, the present high cost of [^{131}I]MIBG makes regular short interval therapy unacceptable in many centres, although the cost compares favourably with some chemotherapeutic regimen and should reduce with more widespread usage. In the future, it may be possible to identify tumor markers that correlate with positive [^{131}I]MIBG uptake and also to explore the possibility of increasing [^{131}I]MIBG uptake using other agents.

This study confirms, therefore, that [^{131}I]MIBG is taken up into known primary and metastatic tumor in some patients with MCT. There is a high incidence of false-negative studies, however, but further work is indicated to evaluate the therapeutic potential of this radiopharmaceutical, in view of the palliative response observed in this study.

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REFERENCES

1. Wieland DM, Wu JL, Brown LE, et al. Radiolabelled adrenergic neuroblocking agents: adrenomedullary imaging with iodine-131-meta-iodobenzylguanidine. *J Nucl Med* 1980; 21:349–353.
2. Trennor J, Feine U, Neighammer D. Scintigraphic imaging of neuroblastoma with ^{131}I metaiodobenzylguanidine. *Lancet* 1984; i:333–334.
3. Geatti O, Shapiro B, Sisson J, et al. Iodine-131 metaiodobenzylguanidine scintigraphy for the location of neuroblastoma: preliminary experience in ten cases. *J Nucl Med* 1985; 26:736–742.
4. Fischer M, Kamanabroo D, Sondorkamy H, et al. Scintigraphic imaging of carcinoid tumours with ^{131}I-metaiodobenzylguanidine. *Lancet* 1984; ii:165.
5. Connell JMC, Hilditch TG, Elliott A, et al. ^{131}I MIBG and medullary carcinoma of the thyroid. *Lancet* 1984; ii:273–274.
6. Endo K, Shiomi K, Kasagi K, et al. Imaging of medullary thyroid cancer with ^{131}I-MIBG. *Lancet* 1984; ii:233.
7. Sane T, Fukanaqa M, Otsuka N, et al. Metastatic medullary thyroid cancer: localization with iodine-131-metaiodobenzylguanidine. *J Nucl Med* 1985; 26:604–608.
8. Poston GJ, Thomas AMK, Macdonald DWR, et al. ^{131}I-MIBG uptake by medullary carcinoma of thyroid. *Lancet* 1985; ii:560.
9. Coutris G, Talbot JN, Kabla G, et al. Uptake of ^{131}I-MIBG by medullary carcinoma of thyroid in familial cases. *Eur J Nucl Med* 1986; 12:77–79.
10. Hilditch TE, Connell JMC, Elliott AT, et al. Poor results with technetium-99m (V) DMSA and iodine-131 MIBG in the imaging of medullary thyroid carcinoma. *J Nucl Med* 1986; 27:1150–1153.
11. Mangner TJ, Tobes MC, Wieland DW, et al. Metabolism of iodine-131 metaiodobenzylguanidine in patients with metastatic pheochromocytoma. *J Nucl Med* 1986; 27:37–44.