*Hospital Topics***New approach to the localisation of phaeochromocytoma: imaging with iodine-131-meta-iodobenzylguanidine**

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Abstract

Thirty eight patients with known or suspected phaeochromocytoma were studied by radioisotope imaging after intravenous administration of iodine-131-meta-iodobenzylguanidine (^{131}I -mIBG), a radiopharmaceutical which has affinity for chromaffin tumours. Seventeen positive results (including one false positive) and 21 negative results (including two false negatives) were obtained. Clinical accuracy was 92%. Urinary noradrenaline concentrations were raised in all patients with confirmed phaeochromocytoma.

These findings show that ^{131}I -mIBG is of value in localising and assessing the extent of chromaffin tumours.

Introduction

Iodine-131-meta-iodobenzylguanidine (^{131}I -mIBG) has been shown to be concentrated in chromaffin tissue, and imaging with a gammacamera can localise phaeochromocytoma in man.¹⁻⁴ This non-invasive investigation is a promising addition to the management of this potentially lethal condition. We present the results of ^{131}I -mIBG imaging and measurement of urinary catecholamine concentrations in 38 patients.

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Patients and technique

Patients were referred for localisation and confirmation of phaeochromocytoma suspected clinically and biochemically, for investigation of suspected recurrent tumour, or for assessment of the extent of malignancy. Thirty seven patients were referred from hospitals in England and Wales, and one from France.

Meta-iodobenzylguanidine sulphate was prepared from meta-iodobenzylamine and cyanamide⁵ and purified by recrystallisation. Administration to Sprague-Dawley rats of 1200 times the equivalent dose in man gave no evidence of sublethal toxicity or mortality. Labelling with ^{131}I was carried out by a modified solid phase method.⁶ Patients were investigated either in hospital or as outpatients over four or five days. Labelled mIBG was administered on day 1 by slow intravenous injection over several minutes, with patient monitoring. On days 2, 3, and 4 images were obtained of the head and neck, thorax, abdomen, and pelvis in the anterior and posterior positions using a wide field of view gammacamera with data acquisition. Carefully positioned marker sources permitted precise orientation of each of the eight views from one day to the next.

Most patients received 20 MBq (0.5 mCi) ^{131}I -mIBG for imaging. Higher activities were administered to patients with known malignant phaeochromocytoma and to some with extra-adrenal tumours. One was studied with ^{123}I -mIBG. Two patients were subjected to repeat imaging, and two with malignancy were treated with high activity ^{131}I -mIBG.

Sequential 24 hour urine collections were analysed for urinary free noradrenaline, adrenaline, and dopamine concentrations using high performance liquid chromatography with electrochemical detection.⁷

Results

Tables I and II give details of a sample of the patients studied.

IMAGING

All patients showed the reported normal tissue distribution of ^{131}I -mIBG in liver, spleen, bladder, salivary glands, and other tissues.⁸ In none was the normal adrenal medulla perceived. Of the 38 patients, 17 showed evidence of positive ^{131}I -mIBG localisation and 21 showed

TABLE 1—Clinical and biochemical details of patients with positive localisation of tumour with ¹³¹I-meta-iodobenzylguanidine (¹³¹I-mIBG)

Case No	Age and sex	Urinary excretion (μmol/24 h)			¹³¹ I-mIBG uptake	Duration and site of disease	Comment
		Noradrenaline (* < 0.47)	Adrenaline (* < 0.11)	Dopamine (* < 2.6)			
Malignant tumours							
1	53 F	9.0	0.77	27.3	Both adrenals, liver, skeleton	8 months; adrenals, widespread metastases	Established diagnosis and extent
2	50 F	20.0	0.13	17.9	Chest, abdomen, skeleton	2 years; abdominal and thoracic tumour masses, bone metastases	Established extent
3	37 M	37.6	0.26	36.2	Abdomen, skeleton	23 years; bladder primary resected, bone metastases	Unsuspected metastases detected
4	18 F	160.3	1.0	14.6	Abdomen, skeleton	10 years; widespread bone metastases	Extent established
5	25 M	3.2	0.06	1.6	Chest, skeleton	7 years; thoracic primary	Unsuspected metastases detected; imaging repeated to monitor progression
6	25 F	0.8	0.07	1.6	Abdomen (3 sites)	2 years; lymph node metastases	Established extent of abdominal spread
7	45 F	2.2	0.02	7.1	Chest, neck, skeleton	1 year; left adrenal (resected), soft tissue metastases	Poor uptake of mIBG; confirmed known extent
8	30 M	2.6	0.03	1.3	Skeleton	6 years; duodenal and abdominal nodes (resected), bone metastases	Monitoring of tumour progression
Benign tumours							
9	57 M	1.7	0.35	2.1	Both adrenals	4 years; bilateral adrenal (neurofibromatosis)	Resected
10	38 F	1.9	0.04	1.4	Mediastinum	3 years; primary benign mediastinal tumour	Resected
11	54 M	0.6	0.36	1.3	Left adrenal	2 years; benign, solitary	Resected
12	70 F	2.1	0.02	0.8	Right adrenal	3 years; benign (neurofibromatosis)	Resected
13	17 F	6.9	0.03	1.8	Mediastinum	2 years; benign—attached to left atrium	Solitary tumour confirmed
14	11 M	1.6	0.02	0.8	Right adrenal	4 years; left adrenal (resected), right adrenal	Resected
15	41 M	3.1	2.07	2.5	Left adrenal	3 years; benign, solitary	Resected
16	41 F	2.2	0.07	0.9	Abdomen	3 years; benign, solitary; lower pole left kidney	Resected

*Upper limit of control range.
Conversion: SI to traditional units—Noradrenaline: 1 μmol/24 h ≈ 169 μg/24 h. Adrenaline: 1 μmol/24 h ≈ 183 μg/24 h. Dopamine: 1 μmol/24 h ≈ 153 μg/24 h.

TABLE 2—Clinical and biochemical details of patients with insufficient follow up or with false negative or false positive results on imaging with ¹³¹I-meta-iodobenzylguanidine (¹³¹I-mIBG)

Case No	Age and sex	Urinary excretion (μmol/24 h)			¹³¹ I-mIBG uptake	Duration and site of disease	Comment
		Noradrenaline (* < 0.47)	Adrenaline (* < 0.11)	Dopamine (* < 2.6)			
17	42 M	0.3	0.14	9.4	? Left adrenal; repeat imaging—normal uptake	3 years	Resection, hyperplasia; symptoms persisting, false positive
18	50 M	3.0	0.06	0.2		2 months; right benign, adrenal	Resected, false negative
19	43 M	15.4	6.50	2.5		4 months; right benign, adrenal	Resected, false negative
20	19 F	13.1	0.16	1.9		1 year; ? site	Clinical evidence, insufficient follow up

*Upper limit of control range.
Conversion: SI to traditional units—Noradrenaline: 1 μmol/24 h ≈ 169 μg/24 h. Adrenaline: 1 μmol/24 h ≈ 183 μg/24 h. Dopamine: 1 μmol/24 h ≈ 153 μg/24 h.

no abnormal concentration. Of the patients with positive imaging results, four (two with malignant disease) were normotensive and not receiving treatment. Uptake by the tumour was usually maximal at 24-48 hours but varied in intensity. In most cases accumulation was well above that of normal hepatic activity, but in others it was less and in some was barely perceptible. Uptake was unrelated to size, location, or malignancy of the tumour.

Patients with positive localisation—Table I gives details of the 16 patients with true positive results. Eight of these patients had malignant phaeochromocytoma, four benign solitary tumours in the adrenal gland (one a recurrence), one bilateral adrenal tumours, and three benign ectopic tumours (two mediastinal and one abdominal). Figure 1 shows examples of the images obtained in these cases. One hypertensive patient (case 17; table II) had suspicious uptake in the region of the left adrenal, and a tumour was confirmed by computed tomography; only minimal hyperplasia was found at surgical exploration, and a second ¹³¹I-mIBG study failed to confirm the initial findings.

Patients with negative imaging results—Twenty one patients showed no abnormal concentration of ¹³¹I-mIBG. One of these had had a phaeochromocytoma resected previously and had a mild recurrence of symptoms. The remainder were new referrals with suspicious clinical and biochemical findings. Eighteen patients with negative results had normal urinary catecholamine concentrations and on follow up showed no definite evidence of phaeochromocytoma. The remaining three patients (cases 18, 19, and 20; table II) had increased excretion of either noradrenaline or adrenaline or both. Subsequently two of these (cases 18 and 19) were found to have benign tumours in the right adrenal. Follow up was incomplete in the third patient (case 20).

Clinical accuracy—Based on the 16 confirmed positive and one false positive result and the 18 true negative and two false negative results

(case 20 being excluded for lack of follow up information) sensitivity of the technique was 89%, specificity 95%, and clinical accuracy 92%.

Quantification of tumour uptake—Concentration of mIBG was estimated from in vivo gammacamera measurement and from assay of the radioactive content of four excised tumours. Benign tumours concentrated up to 2% of injected activity, while some 10 times this amount was taken up by the malignant tumours of the two patients with the highest uptake.

BIOCHEMICAL STUDIES

Figure 2 compares the patterns of excretion of noradrenaline, adrenaline, and dopamine from patients with both benign and malignant tumours (cases 1-16).

All patients with positive ¹³¹I-mIBG imaging results had raised urinary concentrations of noradrenaline. Adrenaline excretion in patients with malignant tumours (cases 1-8) ranged from normal to seven times the upper limit of normal. When adrenaline concentrations were increased, however, the relative increase in noradrenaline excretion was considerably greater. In patients with benign disease four out of seven of the intra-adrenal tumours occurred in association with increased adrenaline excretion, whereas this was normal in all those with extra-adrenal tumours.

Of the eight patients with malignant phaeochromocytoma, five had urinary dopamine concentrations greater than 6.5 μmol/24 h (1000 μg/24 h). All five patients had aggressive malignancy, and three later died. The other three patients (with evidence of skeletal or lymph node deposits) had normal dopamine excretion and a much more benign progression (in two there was no change in the ¹³¹I-mIBG images over one year). Dopamine excretion was also increased in the single patient with a false positive result (case 17); its origin was unknown.

FIG 2—Urinary noradrenaline, adrenaline, and dopamine excretion of patients with true positive localisation of tumour with ^{131}I -meta-iodobenzylguanidine (cases 1-16).

● Malignant. ○ Benign. Vertical dashed line represents upper limit of normal.

Conversion: SI to traditional units—Noradrenaline: $1\ \mu\text{mol}/24\ \text{h} \approx 169\ \mu\text{g}/24\ \text{h}$. Adrenaline: $1\ \mu\text{mol}/24\ \text{h} \approx 183\ \mu\text{g}/24\ \text{h}$. Dopamine: $1\ \mu\text{mol}/24\ \text{h} \approx 153\ \mu\text{g}/24\ \text{h}$.

Discussion

Computed tomography is the most accurate imaging technique at present for localising tumours within the adrenal gland.⁹⁻¹² It is more sensitive and specific than intravenous urography and less invasive than arteriography. Ultrasound is less accurate at detecting tumours¹³ and may not always show the normal adrenal, particularly the left.¹⁴ It is less certain how accurate these techniques are for showing chromaffin tumours sited outside the adrenal gland, or for multifocal or malignant tumours. Our results indicate that ^{131}I -mIBG has considerable promise for the management of patients with phaeochromocytoma. It is taken up by most phaeochromocytomas regardless of site, and screening with the gammacamera readily localises the tumour.

The mechanism of uptake of mIBG is thought to be similar to that of noradrenaline storage in chromaffin tissue. Studies in animals show that uptake is not influenced by drugs commonly used for treatment but that reserpine¹⁵ and tricyclic antidepressants¹ have an inhibitory effect. So far there is no known pharmacological or other method for enhancing the uptake or retention of mIBG by chromaffin tumours.

All but one of our patients with malignant phaeochromocytoma had bone metastases, and we find radioisotope skeletal imaging with technetium-99m methylene diphosphonate valuable in establishing a diagnosis of malignancy, particularly as this cannot be done on histological grounds.

Much has been written on the relevance of catecholamine excretion patterns in patients with phaeochromocytoma.¹⁶ Raised urinary concentrations of adrenaline usually indicate an intra-adrenal tumour. This was true for four of our patients, though three others had normal values. One possible reason for this impaired conversion of noradrenaline to adrenaline is poor induction of phenylethanolamine-N-methyltransferase by adrenocortical steroids,¹⁷ possibly due to impaired blood flow in the tumour.

This study confirms that urinary dopamine concentrations cannot be used to diagnose malignancy.¹⁸ Nevertheless, normal values in three of our patients with known metastases correlated with "benign" progression of the disease. Conversely, patients with "aggressive" malignancy had raised values, one patient excreting normal amounts initially but having a high value shortly before death. This suggests that dopamine excretion might be used as a prognostic sign in the progression of malignant phaeochromocytoma.

We cannot explain the false negative ^{131}I -mIBG imaging results. Tumour turnover of catecholamines may be rapid,¹⁹ and possibly the residence time of the radiopharmaceutical within these tumours was too short for successful imaging.

Labelled mIBG has also been used to treat patients with malignant phaeochromocytoma.²⁰ Two of our patients (cases 1 and 2) received therapeutic doses. The first patient already had advanced malignancy, and administration of mIBG did not alter the progression of this and she died. The second patient showed some symptomatic response but there was no alteration in catecholamine concentrations or tumour bulk. It is too early to anticipate the value of this approach in the treatment of malignant phaeochromocytoma.

Administration of mIBG has two potential hazards. Firstly, it may have a pharmacological effect by displacing catecholamines from tumour tissue. We used 0.2 mg for most imaging studies and up to 6 mg as a therapeutic dose. No adverse effects were observed in any of our patients, and there was no alteration in pulse rate, blood pressure, or temperature after infusion of mIBG. The second potential hazard arises from tissue radiation doses of ^{131}I . The estimated whole body radiation dose from our retention data is approximately 0.04 mGy/MBq (roughly 150 mrad/mCi). Allowing for the errors inherent in such a calculation, this is not significantly different from previous estimates of 0.06 mGy/MBq (roughly 230 mrad/mCi).²¹ Some in vivo breakdown does take place, as evidenced by the appearance of free ^{131}I -iodide in the urine; accumulation of free ^{131}I -iodide in the thyroid is reduced by oral potassium iodide.

In conclusion, ^{131}I -mIBG imaging has considerable promise in the management of patients with chromaffin tumours. It has a place in (a) confirming adrenal phaeochromocytoma when the results of computed tomography are in doubt; (b) identifying recurrent or extra-adrenal phaeochromocytoma; (c) detecting unsuspected multifocal tumours, either within or outside the adrenal; (d) assessing the extent of malignant phaeochromocytoma; and (e) investigating patients with a strong family history of phaeochromocytoma whether or not they have evidence of other endocrinopathy.

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Clinical Algorithms

Weakness

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The algorithm presents a diagnostic approach to patients presenting with, or found to have, some form of weakness. The main diagnostic patterns considered relate to generalised weakness and to both symmetrical and asymmetrical non-generalised weakness, though many causes of symmetrical weakness can also present in an asymmetrical fashion. By its very nature an algorithm gives relatively stark information and permits little scope for considering the mode of presentation and history, both of which may give important pointers to diagnosis. Most of the diagnostic suggestions are indications for referral to a specialist.

Patients often include generalised weakness among their presenting symptoms. Generalised weakness is often due to underlying systemic disease or a neurotic or depressive problem and has a more specific cause only in rare cases. When weakness is not generalised the pattern of disability is of great diagnostic importance. Hemiparesis is a familiar presentation and is usually, but by no means always, due to cerebrovascular disease. Alternative causes should be sought in younger and atypical patients. Certain neurological disorders, such as multiple sclerosis or motor neurone disease, show patterns that evolve gradually, and the diagnosis may therefore not be apparent at the time of initial presentation. When dealing with weakness in the legs clinicians should always consider the possibility of cord compression as immediate myelography and subsequent laminectomy will prevent paraplegia in many cases. Fully developed subacute combined degeneration of the cord is only rarely seen, and clinicians should be critical of accepting this diagnosis rather than arranging myelography. Though much rarer than in the past, neurosyphilis still occasionally develops, and many would still consider

serological screening to be a worthwhile routine investigation in patients with neurological complaints, particularly as the meningo-vascular form may respond dramatically to treatment with penicillin.

The problem often arises of distinguishing between an organic and a neurotic basis for a particular patient's complaint of weakness. This may be extremely difficult, and, though certain features can be helpful, none should be regarded as foolproof. Patients with neurosis often show an inappropriate indifference to their disability. They may show inconsistencies in their weakness, being unable, for example, to move a leg while under examination yet walking quite normally when less closely observed. Inconsistencies may also appear in the history if, for example, a patient has a paralysed arm but no difficulty in wearing lace up shoes. A patient with neurosis is also likely to have a sharply demarcated region of motor and sensory failure that is anatomically incompatible with an organic neurological lesion. There may be lack of genuine effort in complying with tests of power, often accompanied by tensing of muscles other than those under scrutiny. No matter how many times a neurotic individual "cries wolf," however, this does not render him insensitive to organic disease. Likewise, patients showing obvious features of hysteria may none the less have some underlying organic weakness.

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Further reading

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