Methodology and Dosimetry in Adrenal Medullary Imaging with Iodine-131 MIBG

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Iodine-131 MIBG scans were performed in 59 patients in order to localize intra- or extra-adrenal pheochromocytomas (pheos), or to visualize hyperplastic adrenal medulla. Images were obtained from the pelvis to the base of the skull on Days 1, 4, and 7 after tracer injection. The 15 patients with histopathologic confirmation of adrenal medullary disease had positive scans. In three of these, the pheos were visible only on images obtained on Day 7. One scan was false negative. After excluding patients with a predisposition to adrenal medullary disease, nine subjects (28%) without verification of pheo displayed adrenal uptake of the radionuclide. Late images produce a low rate of false-negative scans; the background activity diminishes and even small pheos can be detected. In order to increase the quality of late images, 40 MBq [^{131}I]MIBG was used instead of 20 MBq. The dosimetric considerations are discussed.

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It has been shown that radioiodine-labeled metaiodobenzylguanidine (MIBG) is taken up by sympathetic tissue and retained to a degree which makes it possible to visualize hyperfunctioning adrenal medulla with a gamma camera (*1–5*). As many as 20% of normal adrenal medullas are reported to be seen (*3*) and 13% of the iodine-131 (^{131}I) MIBG scans are reported to be false negative (*4*).

In 1983, [^{131}I]MIBG became available in Sweden and we started adrenal medullary scintigraphy as described by Shapiro (*2*). After the first 20 scans the impression was that late images increased the diagnostic accuracy. Scintigraphies were performed by systematically obtaining images 7 days after tracer injection, in addition to early images. In order to improve the quality of late images, we raised the administered activity of [^{131}I] MIBG from 20 MBq (0.5 mCi) to 40 MBq (1 mCi).

The purpose of this study is to report our experience of adrenal medullary imaging and of the value of late images, and to report the results of our measurements of percentage uptake and calculations of half-time values in the adrenals.

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METHODS

Patients

Between May 1983 and July 1985 [^{131}I]MIBG scans were performed in 59 patients. Before being referred for scintigraphy, the patients underwent a thorough endocrinologic investigation including the determination of epinephrine, norepinephrine, metoxy-catecholamine, and vanillylmandelic acid (VMA) in 24-hr urine collections.

Forty-one patients were investigated because sporadic pheochromocytoma (pheo) was suspected, 13 MEN-II gene carriers and five patients with neurofibromatosis underwent the investigation, in 14 cases as a screening procedure and four cases because pheo was clinically suspected.

Scintigraphy

The thyroid gland was blocked by giving 100 mg of potassium iodide orally twice a day for 10 days, starting one-half hour before tracer injection.

The first 20 studies were performed after the injection of 20 MBq (0.5 mCi) [^{131}I]MIBG supplied by Institutt for Energiteknikk, Kjeller, Norway. In the subsequent studies 40 MBq (1mCi) [^{131}I]MIBG was used in order to improve the quality of late images.

Images were obtained on Days 1, 4, and 7 using a wide (40 cm) field-of-view gamma camera equipped with a high-energy, parallel hole collimator. The gamma camera was connected to a minicomputer and images were stored for background subtraction, quantification of uptakes, and half-time calculations. Dorsal views from the pelvis to the base of the skull were obtained on Days 1 and 4. On Day 7, a dorsal view of the upper abdominal region was obtained, as well as a view of regions with suspected extra-adrenal uptake. Ventral views of the upper abdominal region were obtained on all imaging occasions. On Days 1, 4, and 7 the acquisition time was 5, 20, and 30 min respectively.

The method of background subtraction and calculation of percentage adrenal uptake are illustrated in Figure 1. The small rectangle includes the adrenal and the larger rectangle minus the smaller represents the background area. The average number of counts per pixel in the background area was assumed to represent the background in the adrenal area. After subtracting the background, the adrenal uptake was calculated by comparison with an adrenal phantom at a depth of 5 cm. The liver uptake was calculated according to the conjugate view technique (*6*).

The uptake of the spleen was calculated from the dorsal view by comparison with a standard spleen phantom (*7*). The salivary gland uptake was calculated from the lateral view by comparison with a phantom.

The thyroid was scanned on Days 1 and 4 and was never visualized. Thus it was not possible to quantify the uptake. The highest possible uptake of radioiodine compatible with nonvisualization with the gamma camera was calculated.

Chromatography

The radioiodine content of samples of the [^{131}I]MIBG batches was determined using gel chromatography. In three patients, the radioiodine content of urine was determined 1, 4, and 7 days after tracer injection.

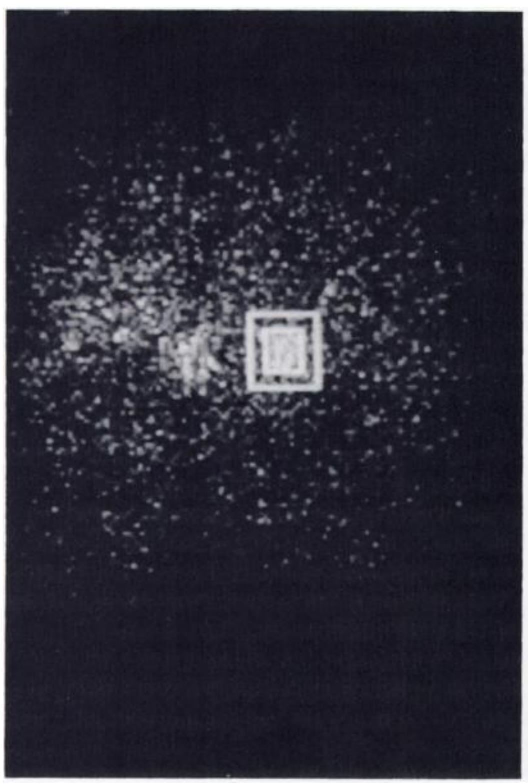

FIGURE 1
Regions of interest for background subtraction and calculation of percentage uptake and half-time of [^{131}I]MIBG in the background and the adrenal. Posterior view.

RESULTS

Classification of Scans

Scans have been classified as negative or positive. Negative scans are those with neither intra-adrenal uptake nor uptake indicating extra adrenal pheo. Positive scans are those with intra-adrenal uptake or those with uptake indicating extra-adrenal pheo. Of the 59 patients included in this study 26 had negative scans and 33 had positive ones.

Negative scans (Table 1) were found in 26 patients; two belonged to one MEN-II A family, one to a family with neurofibromatosis, and the remaining 23 patients were referred to our department for scintigraphy to exclude/verify the presence of a sporadic pheo. Further clinical observation (2.5–4 yr), laboratory investigations and adrenal computed tomographic (CT) scans contradict that 25 of these 26 patients had pheo.

A false-negative scan was obtained in one patient with a large intrahepatic pheo. This tumor was clearly shown by liver scintigraphy and CT. This patient had elevated urinary excretion of catecholamines and metabolites. Partial liver resection confirmed the diagnosis of an intrahepatic pheo with a diameter of 6 cm. Two years after the operation the patient is well and has normal urinary excretion of catecholamines and metabolites.

Positive scans (Table 1) were obtained in 33 patients, 18 sporadic, 11 MEN-II and four neurofibromatosis patients.

Sporadic cases. Of the six cases with unilateral adrenal uptake of [^{131}I]MIBG adrenal pheos could be verified by surgery in four. The remaining two patients with unilateral adrenal uptake had normal catecholamines and negative CT scans. They had previously undergone adrenal surgery, one for adrenal medullary hyperplasia (AMH) and the other for pheo.

Bilateral adrenal exploration and unilateral adrenalectomy were performed in two of the nine patients with bilateral adrenal uptake. One had a pheochromocytoma and the other had AMH (*8*).

The extraadrenal uptake noted in three cases was due to metastases from a malignant pheo in one case, to an intrathoracic pheo in another case and to a pheo in the renal hilus in the third case.

The nine sporadic cases with positive scans but without confirmation of adrenal medullary disease have been followed for 2.5 to 4 yr and all observations indicate that the patients do not have adrenal medullary disease.

MEN-II patients. The six patients with unilateral adrenal uptake had previously been adrenalectomized for pheo. One patient who had a MEN-II B syndrome had the remaining adrenal excised because of a small pheochromocytoma.

Five patients had bilateral adrenal uptake that was

TABLE 1
Results of [^{131}I]MIBG Scanning in 59 Patients

MIBG scan	Sporadic (41 subjects)	MEN II (13 subjects)	Neurofibromatosis (5 subjects)	All n = 59
No adrenal uptake	23*	2	1	26
Unilateral adrenal uptake	6† (4)§	6‡ (1)	1 (1)	13 (6)
Bilateral adrenal uptake	9 (2)	5 (2)	3 (2)	17 (6)
Extra-adrenal uptake	3 (3)	—	—	3 (3)

* One false-negative (intrahepatic pheo).
† Two patients previously unilat. adrenalectomized.
‡ All previously unilat. adrenalectomized.
§ Number of patients with confirmation of pheo or AMH within brackets.

FIGURE 2
Iodine-131 MIBG scan of a patient with neurofibromatosis, without any symptoms or signs of pheochromocytoma. Both adrenals are visualized, and the adrenals become more visible with time as the background activity diminishes. The patient has not had surgery so there is no confirmation of diagnosis. Posterior view.

asymmetric in two of them, these two patients had each a small unilateral pheo removed.

Patients with neurofibromatosis. One patient had a unilateral uptake corresponding to a large pheo. Three patients had bilateral asymmetric uptake. One of these patients had bilateral tumors and another had unilateral AMH. The third patient has normal catecholamines but a CT scan has revealed a small tumor in the adrenal with the greatest uptake. This patient has been offered surgery but has declined the offer (Fig. 2).

Evaluation of Positive Scans with Confirmation of the Diagnosis

The details of scans of the 12 patients with histologically verified intra-adrenal pheo or AMH have been studied and Figure 3 summarizes our findings. One tumor was visible only on images obtained on Day 1. Three small adrenal tumors ranging in weight from 2 to 10 g were visible only on images obtained on Day 7. Six pheos were visualized on all imaging occasions and the uptake in the remaining three cases, including the two AMH cases, was seen on Day 4 and Day 7. All uptake, except that visible only on Day 1, was increasingly vivid up to Day 7 (Fig. 4).

The percentage uptake of [^{131}I]MIBG for Day 4 and Day 7 was used, after background subtraction, for calculating the effective half-time of [^{131}I]MIBG in the

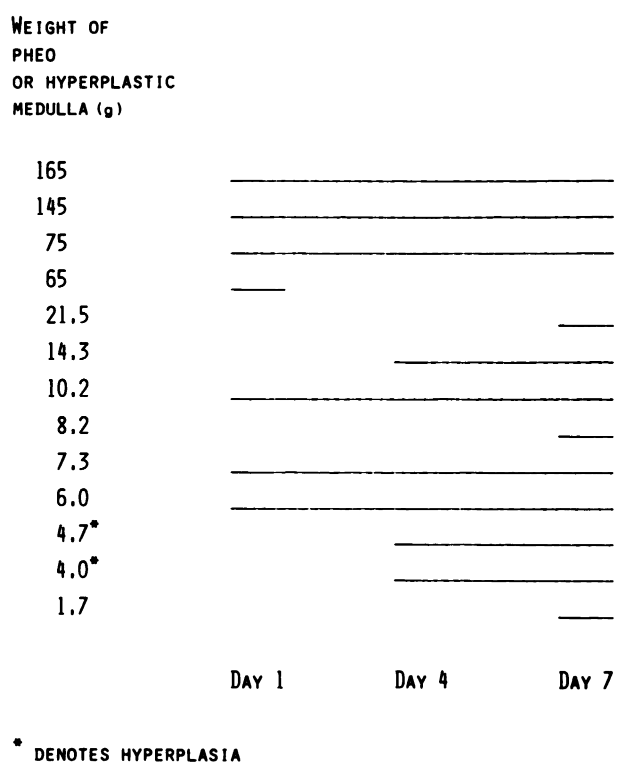

FIGURE 3
Day after [^{131}I]MIBG injection on which pheos (11) or hyperplasias (2) were visualized in 12 patients.

FIGURE 4
Iodine-131 MIBG scan of a patient who belongs to a MEN-11A family and who has had surgery for a left-sided pheo weighing 14 g. Posterior view.

adrenals. The effective half-time of the background was also calculated (*9*). Our measurements show that 95.5% of the background activity has a half-time of 28 hr and 4.5% has a half-time of ~8 days (i.e., the half-life of ^{131}I). Figure 5 shows how the quotient between adrenal and background activity changes with time in (a) a case with a half-time of [^{131}I]MIBG in the adrenals of 100 hr and (b) a case with a half-time in the adrenals of 70 hr. The calculations are based on the assumption of an initial adrenal [^{131}I]MIBG uptake of 36 cpm (0.03% of injected activity) over an area of 3 × 3 cm and a background activity of 680 cpm over the same area. In most cases the effective half-time of [^{131}I]MIBG in pathological adrenal tissue exceeded that of the background and this explains why the adrenals were increasingly vivid with time after tracer injection.

Table 2 summarizes our calculations of percentage uptake and percentage uptake per gram of tumor tissue (%/g). Percentage uptake was based on in vivo measurements using the gamma camera and not on measurements on surgical specimens. The values for %/g uptakes are extrapolated to time zero after tracer injection from measurements of uptake on Day 4 and Day 7.

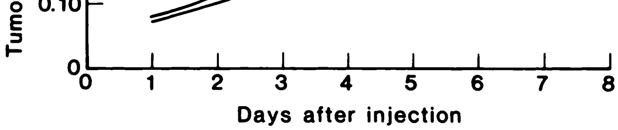

FIGURE 5
Two theoretical cases of [^{131}I]MIBG uptake with a half-time of a) 100 hr and b) 70 hr. On the y-axis the quotient between the netto uptake in the adrenals and the background uptake is given. When the quotient exceeds 0.20 (adrenal uptake 20% above background) the adrenal uptake usually is visible. The curves show that the quotient increases with time, the half-time of the background being less than that of the adrenals.

TABLE 2
Percent Tumor Uptake of [^{131}I]MIBG and Percent Tumor Uptake per gram Tumor Tissue (%/g)*

Tumor weight (g)	Percent uptake of injected activity	Percent uptake per gram tumor tissue (%/g)
1.7	0.044	0.026
6.0	0.023	0.0038
7.3	0.28	0.038
8.2	0.076	0.0093
10.2	0.18	0.018
14.3	0.018	0.0013
21.5	0.072	0.0033
75.0	1.3	0.017

* Data were available for eight pheos from seven patients. The values are extrapolated to time 0 from measurements of uptake on Day 4 and Day 7.

Dosimetry and Chromatography

Table 3 summarizes the results of our calculations of absorbed radiation doses in the liver, spleen, salivary glands, adrenals, and thyroid after the injection of 40 MBq [^{131}I]MIBG. These results have been reported

TABLE 3
Calculated Absorbed Radiation Doses in Different Organs (*9*)

Organ	Absorbed radiation dose mGy/MBq (0.1 rad/MBq)
Liver	0.83
Spleen	0.61
Salivary glands	0.22
Adrenals*	0.2
Thyroid	0.1

* The absorbed radiation dose in the normal adrenal medulla may be 10 times higher than in the whole adrenal as the mass of the medulla is only ~1/10 that of the adrenal (*8*).

earlier (*9*). The different organs are listed in order of falling absorbed radiation doses. The highest dose was found in the liver (0.83 mGy/MBq) and the lowest in the thyroid (0.1 mGy/MBq). The calculated absorbed radiation dose in adrenals with a positive scan but without confirmation of diagnosis was 0.2 to 1.7 mGy/MBq. Consequently, it is assumed that patients with a negative scan have an absorbed radiation dose in the adrenals of <0.2 mGy/MBq (*9*).

Measurements of the iodide content of the [^{131}I]MIGB tracer batch showed the free radioiodide content to be 1% or less. Urinary content of free radioiodide was found to be 5% or less of the total radioiodine activity, thus indicating the in vivo liberation of radioiodine from [^{131}I]MIBG.

DISCUSSION

This study shows that late images are of great value; pheos with low percentage uptake are seen when background activity has practically ceased. In 15 patients in this series there was histologic verification of hyperfunctioning tissue accumulating [^{131}I]MIBG. Three small pheos were visible only on images obtained on Day 7 and all pheos, except the one visible only on Day 1, were increasingly vivid up to Day 7 after tracer injection, due to a longer half-time of [^{131}I]MIBG in the adrenal medulla than in the background (Figs. 2 and 4). One false-negative scan was found in this study; this is less than the figure reported by others (*4,5*). An explanation of the higher frequency of false-negative scans in other series could be that imaging has been performed only up to Day 3.

After excluding patients with a predisposition to adrenal medullary disease, i.e., those with MEN-II syndromes, von Recklinghausen's neurofibromatosis and previously known AMH, nine subjects without verification of pheo had adrenal uptake of [^{131}I]MIBG. In most of these nine patients the adrenal uptake was faint. These nine patients and those sporadic cases with negative scans have been followed up for 2.5 to 4.5 yr without signs or symptoms indicating the presence of a pheo. The occurrence in this study of positive scans in 28% of patients who in all likelihood do not have pheos is more than the 13 to 20% found in "normal" subjects in other studies (*3,10*). However, in this as in other series, symptomatic patients were investigated. As a result we still do not know what the occurrence of adrenal uptake is in a group of normal controls.

The reported superiority of iodine-123 (^{123}I) MIBG over [^{131}I]MIBG (*11*) as a result of better counting statistics is true only if imaging is confined to between 40 and 48 hr after tracer injection. If it is accepted that late images are of value, [^{123}I]MIBG cannot be used due to its short half-life (13 hr). The short half-life further limits the availability of [^{123}I]MIBG as its use is confined to centers where the compound can be synthesized on the day of injection. Another disadvantage of [^{123}I]MIBG is that it costs 5 to 10 times more than [^{131}I]MIBG (*11*). So, despite the photon energy peak at 159 keV and the absence of beta energy, [^{123}I]MIBG is of less value than [^{131}I]MIBG in adrenal medullary imaging where it is important with late images, when background activity is reduced to a minimum (*9*).

At the beginning of this study when we used 20 MBq [^{131}I]MIBG, we found that it was difficult to evaluate late images due to the counting statistics. To improve the quality of late images more activity than usually recommended is necessary (*2–5*). In our experience 40 MBq (1 mCi) [^{131}I]MIBG is sufficient. As seen in Table 3 the absorbed radiation dose of the thyroid is 0.1 mGy/MBq. The explanation of this low dose is the effective blocking of the thyroid with potassium iodide (*12*), the low content of free radioiodide in the MIBG tracer batch, and the low percentage in vivo liberation of radioiodide. The absorbed radiation dose in the adrenal gland without a pheo is ~0.2 mGy/MBq and about ten times higher in the adrenal medulla (Table 3). From 40 MBq [^{131}I]MIBG the adrenal medulla dose is ~80 mGy (8 rad) and possibly sometimes as high as 700 mGy. When judging the hazards of this dose as well as other organ doses the low dose rate of ^{131}I must be remembered. The total absorbed radiation dose of 80 mGy is achieved with a dose rate of less than a thousandth Gy/min decaying to zero over several days (*13*). There is no knowledge of the risks of this type of radiation on the adrenals. Holm (*14*) studied the effect of diagnostic and therapeutic radioiodine doses on the thyroid and found no evidence of tumor induction. Fjälling et al. (*15*) studied the effect on the parathyroids of radioiodine trapped in the thyroid and found no evidence of the induction of parathyroid disease. In vitro studies of the survival of rat thyroid cells after exposure to ^{131}I and x-rays have shown that ^{131}I has ~ 1/10 the effect of external x-rays (*16,17*). There is also the clinical observation that 10–20 Gy of external radiation has the same remission rate on thyrotoxicosis as 60–150 Gy of internal radiation from ^{131}I (*18, 20*).

Considering these biologic observations of the different effects of radioiodine and external x-rays on the thyroid and parathyroids, we think that it is realistic to assume that there are analogous differences in the effects of radioiodine and x-rays on other organs including the adrenals. The potential danger of a pheochromocytoma far outweighs the probably negligible risks of the adrenal medulla radiation dose from radioiodine. For adrenal medullary scintigraphy we therefore recommend administering 40 MBq [^{131}I]MIBG to make late images possible.

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