

# MIBG Scintigraphy

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## 1. Introduction

Intravenous administration of  $^{131}\text{I}$  or  $^{123}\text{I}$ -labeled iobenguane or meta-iodobenzylguanidine (MIBG) is followed, after varying intervals, by scintigraphic images of the whole body. The aim is to detect tumours that originate from the neural crest or to study abnormalities/disturbances of the sympathetic nervous system.

MIBG is an aralkylguanidine produced from 2 anti-hypertensives. This is achieved by combining the benzyl group of bretylium and the guanidine group of guanethidine, with iodine at the meta position. The uptake mechanism is based on specific characteristics of abnormal neural crest cells; namely an active, sodiumdependent, saturable absorption mechanism in the cell membrane, as well as storage in neurosecretory granules in the cytoplasm. Because of the specific retention of MIBG in these cells, the abnormality will, over time, become more clearly distinguishable from normal tissue which does not have this mechanism.

## 2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

## 3. Indications

- a. Detection of tumours which originate from the neural crest: pheochromocytomas, paragangliomas, chemodectomas, ganglioneuromas. Detection, staging and follow-up of neuroblastomas.
- b. To determine whether a carcinoid or medullary thyroid carcinoma should be treated with  $^{131}\text{I}$ -MIBG.
- c. To determine whether there is MIBG-inclusion in the following tumours: neurofibromatosis, retinoblastoma, aesthesioneuroblastoma, schwannoma, Merkel-cell tumour, islet cell tumour (pancreas), small cell lung carcinoma, melanoma.
- d. To test the function of the adrenal medulla (hyperplasia), myocardium (sympathetic innervation), lungs (endothelial function) and salivary glands (sympathetic innervation).
- e. Post-treatment scintigraphy after high dose  $^{131}\text{I}$ -MIBG.

## 4. Relation to other diagnostic procedures

MIBG-scintigraphy and CT scanning are both very sensitive means of demonstrating an intra-adrenal pheochromocytoma. CT shows more anatomical detail, but the MIBG scintigram allows a more specific statement about the nature of the disease.

MIBG scintigraphy is preferred in the analysis of extra-adrenal and malignant pheochromocytoma (metastases). In general, the findings on an MIBG scintigram correspond to the excretion of catecholamine degradation products in the urine.

However, this is not the case for neuroblastomas. The pathological findings on the MIBG scintigram of a neuroblastoma do not always correspond to the observed excretion of catecholamines or catecholamine metabolites in the urine and are not always consistent with the findings of the bone marrow aspiration.

Confirmation of lesions found using ultrasound/CT scan/MRI is desirable and aids in tumour volume determination for dosimetric purposes.

For carcinoid, the findings of the MIBG scintigram are not clearly correlated with the amount of 5-HIAA excretion in urine. Correlation with somatostatin receptor scintigraphy (higher sensitivity) may determine the choice of therapy.

Well differentiated neuroendocrine tumours will procure more reliable (or more specific) results from MIBG and somatostatin receptor scintigraphy as compared to  $^{18}\text{F}$ -FDG PET.

New PET tracers, such as  $^{68}\text{Ga}$ -DOTATATE,  $^{68}\text{Ga}$ -DOTANOC and  $^{18}\text{F}$ -DOPA, are now available for detection of neuroendocrine tumours. Both sensitivity and specificity are much higher than those reported for MIBG or Octreotide scintigraphy. The advantage of MIBG scintigraphy over the newer techniques is the close correlation with catecholamine production. There fore allowing image guided therapy. The combination of MIBG scintigraphy and other tracers or techniques such as MRI and CT is of value in patients with metastasized neuroendocrine tumours to assess whether therapy with  $^{131}\text{I}$ -MIBG is indicated or not. In this respect, multifocality and knowledge of uptake at all sites is important to assess the therapeutic effect and overall outcome.

$^{123}\text{I}$ -MIBG myocardial scintigraphy with quantification provides prognostic information in patients with cardiac failure due to cardiomyopathy and a left ventricular ejection fraction < 35%. This specific information cannot be obtained with other techniques. Due to the relative high costs of this technique, follow-up LVEF measurements may already be indicative for recovery or not, especially in oncological practice. Therefore, follow-up LVEF measurements for cardiotoxicity due to chemotherapy is still standard practice. In nuclear cardiology,  $^{123}\text{I}$ -MIBG scintigraphy has a clear, established role.

### 5. Medical information necessary for planning

- a. Medication in use.
- b. In pheochromocytoma: symptoms, blood pressure, VMA in urine.
- c. In neuroblastoma: known tumour sites, age, weight, bone marrow aspiration, urine test for catecholamines and catecholamine breakdown products and whether  $^{131}\text{I}$ -MIBG therapy is being considered.
- d. In carcinoid: symptomatology (carcinoid syndrome), 5-HIAA in urine.
- e. In medullary thyroid carcinoma: symptomatology, calcitonin and CEA content in serum.
- f. In all tumours: known sites and how demonstrated.
- g. In cardiology: results of other cardiological tests, left ventricular ejection fraction, history of events and interventions, chemotherapy or use of cardiotoxic drugs

### 6. Radiopharmaceutical

Tracer:  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) or  $^{131}\text{I}$ -MIBG

Nuclide: Iodine-131, Iodine-123

- Activity:** 40-80 MBq  $^{131}\text{I}$ -MIBG; 185-370 MBq  $^{123}\text{I}$ -MIBG. The activity administered to children should be calculated on the basis of a reference dose for an adult, scaled to body weight according to the schedule proposed by the EANM Paediatric Task Group ( $^{123}\text{I}$ -MIBG 80-400 MBq). In case of post-treatment scintigraphy, the standard administered activity ranges from 3700-7400 MBq.
- Administration:** Slow intravenous injection; i.e. over a period of 1 min. Care needs to be taken to avoid extravasation of  $^{131}\text{I}$ -MIBG. With too rapid administration, symptoms of palpitations, dyspnoea, raised pressure, sensations of warmth, flushing (with carcinoid) and abdominal pain may occur.
- Choice:** For function-testing (indication 2d):  $^{123}\text{I}$ -MIBG. For detection of pheochromocytoma and paraganglioma, and for detection and follow-up of neuroblastoma,  $^{123}\text{I}$ -MIBG is preferred, because of its imaging characteristics and the possibility of SPECT.  $^{131}\text{I}$ -MIBG is still indicated when late exposures (after 48 and 72 h) are undesirable (e.g. in slowly absorbing tumours, tumour sites in or near the liver, assessment of retention in preparation for  $^{131}\text{I}$ -MIBG therapy).

### 7. Radiation safety

Clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure in patients known or suspected to be pregnant. If possible, MIBG scintigraphy should be postponed after delivery. Breast feeding should be interrupted for at least 3 weeks according to ICRP 106. Renal insufficiency: Plasma clearance of  $^{123}\text{I}$ -MIBG is reduced in patients with renal insufficiency.  $^{123}\text{I}$ -MIBG is not cleared by dialysis.

The effective doses are 0,013 mSv/MBq for  $^{123}\text{I}$ -MIBG and 0,14 mSv/MBq for  $^{131}\text{I}$ -MIBG in adults. There is an increased radiation dose from CT in SPECT/CT protocols (volume CT dose index: 3-5 mGy depending on acquisition parameters).

### 8. Patient preparation/essentials for procedure

- The following medication should be discontinued in any case: reserpine, cocaine, tricyclic antidepressants, calcium channel blockers, labetalol, tranquilizers (especially phenothiazines). In the literature, more potential sources of interference are mentioned which should be taken into account.
- Blocking of unintentional radioactive iodine uptake in the thyroid by administration for 5-10 days ( $^{131}\text{I}$ -MIBG) or 2-3 days ( $^{123}\text{I}$ -MIBG) of sodium or potassium iodide (100-150 mg per day) or sodium or potassium perchlorate (200-400 mg per day) starting the day before administration of the radiopharmaceutical.

#### *Requirements for carrying out the examination*

Standard solution  $^{131}\text{I}/^{123}\text{I}$  and perspex phantom for measurement of the standard, if preparation for therapy is taking place.

## 9. Acquisition and processing

### *General aspects:*

- Allow patient to urinate shortly before the exposures.
- Views: Supine, whole body anterior and posterior.
- Additional images: possibly lateral exposure; in the case of  $^{123}\text{I}$ -MIBG, possibly tomography.
- Times: When using  $^{123}\text{I}$ -MIBG, 24, 48 and possibly 72 h after administration. When using  $^{131}\text{I}$ -MIBG, 24 h (and possibly 48 h) after administration. When myocardial function testing, after 15 min and 4 h. When post-therapy scintigraphy, after 2-7 days depending on local protocols.
- Processing of data: For purposes of dosimetry (in connection with possible therapy) and using the computer, the amount of activity in the region of interest (ROI) is measured and expressed in % of the administered dose, by comparing counts in the ROI, corrected for background activity, with the counts of a known quantity of  $^{131}\text{I}$  and  $^{123}\text{I}$  (standard), likewise corrected for background. It is preferable that this be carried out both for the anterior and posterior exposures, so that the geometric mean can be calculated. By performing this calculation on sequential images, an impression of the effective half-life ( $T_{1/2, \text{eff}}$ ) can be obtained.

### *Camera settings:*

#### Iodine-131

Energy:	$^{131}\text{I}$ -setting, 364 keV
Window:	20%
Collimator:	HEAP
Counting time:	10 min
Computer:	matrix of 128×128 or 256×256
Total-body scans:	Multiple planar images of the whole body are preferred over whole body images with a running speed of 6 cm/min (matrix size 128×512)

#### Iodine-123

Energy:	$^{123}\text{I}$ -setting, 159 keV
Window:	15-20%
Collimator:	LEHP, LEAP or MEAP
Counting time:	5 min
Computer:	Matrix size 256×256
Total-body scans:	Multiple planar images of the whole body are preferred over whole body images with a running speed of 4-6 cm/min (matrix size 128×512)
SPECT:	24 h after injection. 60 (2×30) exposures, 40 sec/exposure, matrix size 64×64

The imaging session may be completed with a SPECT (SPECT/CT) scan over the anatomical regions showing pathological tracer uptake on planar images. The SPECT images are obtained over a 360° orbit (128×128 word matrix, 6° angle steps, 30-45 sec per stop). Coregistered CT images (100-130 kV, mAs modulation recommended) from SPECT/

CT cameras enable attenuation and facilitate precise localization of any focus of increased tracer.

*Reconstruction:* SPECT iterative reconstruction or reconstruction using another validated protocol that allows accurate visualization of lesions (to be adapted to the clinical setting), and CT-based attenuation correction for SPECT/CT, can also be performed. Attenuation correction can be performed on SPECT images alone based on the constant  $\mu$  before or after processing (e.g. Sorenson, Chang), but it is not usually done. Scatter correction methods using spectral analysis can be used to improve the accuracy of quantification.

*Quantification of myocardial uptake:* The following procedure can be used for assessing myocardial uptake; planar  $^{123}\text{I}$ -MIBG images are analysed using regions of interest to calculate the myocardial uptake ratios and washout percentages (WR). A manually drawn region of interest is the left ventricle, and a rectangular region of interest has to be placed at the mediastinum (nonspecific  $^{123}\text{I}$ -MIBG accumulation). The average counts/pixel are calculated in each region for the early and late images. After correcting for the physical decay of  $^{123}\text{I}$ , the values are used to calculate the early and delayed heart-to-mediastinum ratio (HMR) and the washout rate (WOR).

WOR:  $100\% \times (H-M)_{\text{early}} - (H-M)_{\text{late}} / (H-M)_{\text{early}}$ , where H is the mean counts/pixel in the LV and M is the mean counts/pixel in the upper mediastinum. The results have to be interpreted according to the proposal of the European Association of Nuclear Medicine (EANM) for standardization of  $^{123}\text{I}$ -MIBG scintigraphy.

## 10. Interpretation and pitfalls

- Normal structures into which MIBG is absorbed are: salivary glands, myocardium, adrenal medulla and liver, while as a result of excretion, activity in the bowel and bladder can also be seen.
- Concentrations outside the normal structures should be interpreted as suspicious for a tumour of neural crest origin.
- One should be mindful of contamination, hypertrophy of the remaining adrenal medulla after unilateral adrenalectomy, hydronephrosis, pathology in or near liver, bowel and bladder.
- False-negative results can be obtained when certain medications are used (see patient preparation).
- The results of myocardial uptake quantification have to be interpreted according to the proposal of the European Association of Nuclear Medicine (EANM) for standardization of  $^{123}\text{I}$ -MIBG scintigraphy.

## 11. Report

- The images are evaluated for the existence of pathological activity concentrations corresponding to tumour sites. Changes in distribution and uptake in tumours over time are reported.
- The uptake (% of the dose) and retention (T<sub>eff</sub> in days) in the tumour is stated, if a therapeutic dose must follow.
- In myocardial function testing, uptake pattern, intensity and quantitative values are reported.

## 12. Literature

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