GUIDELINE FOR RADIOIODINATED MIBG SCINTIGRAPHY IN CHILDREN

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Under the Auspices of the Paediatric Committee of the European Association of Nuclear Medicine

I Purpose

The purpose of this guideline is to offer to the Nuclear Medicine team a useful framework in daily practice. The present document is influenced by the conclusions of the reunion on "Consensus Guidelines for MIBG Scintigraphy" (Paris, November 6, 1997) of the European Neuroblastoma Group and by those of the Oncologic Committee of the French Society of Nuclear Medicine [1]. This guideline summarises the views of the Paediatric Committee of the European Association of Nuclear Medicine. It should be taken in the context of "good practice" of nuclear medicine and local regulation.

II Background information and Definitions

Meta-iodobenzylguanidine (MIBG) is an aralkylguanidine noradrenaline analogue which, once iodinated with ^{131}I or ^{123}I, enables successful imaging of neuroectodermally derived tumours, including neuroblastoma and phaeochromocytomas [2-6] although other tumours, such as paragangliomas, medullary thyroid carcinomas, carcinoid tumours, Merkel cell tumours of the skin, and metastases of these tumours, have been shown to take up MIBG [7,8].

Neuroblastoma is one of the most common solid malignant tumours of childhood. As the stage of the disease has an impact on both prognosis and treatment, and as 80% of neuroblastoma are metastatic (stage IV) at the time of presentation, the accurate identification of all lesions is crucial to evaluate the extent of disease [9,10]. The specificity of MIBG for detecting primary and secondary neuroblastoma approaches 100%. The sensitivity in detecting sites on a lesion-by-lesion basis is about 80% and the sensitivity in terms of staging is 90-95% [11-16]. The high tumour affinity also allows the therapeutic use of the ^{131}I labelled compound [17-19]. MIBG therapy shares with MIBG imaging several points but this guideline only covers its use in diagnosis and follow-up. This guideline contains information related to the indications for, acquisition, processing, and interpretation of radioiodinated MIBG scintigraphy in neuroectodermally tumours in order to obtain scans with high and constant quality.

There was controversy regarding the respective value of MIBG and bone scan in neuroblastoma patients. It is

now clear that neither MIBG scintigraphy nor MDP bone scans alone detects all the lesions. In some cases bone scan detects lesions that are MIBG negative and in others MIBG uptake is positive while the bone scan is normal[20]. Thus, initial assessment should include both MDP bone scan and MIBG scintigraphy. MIBG assesses response to treatment of primary tumour and metastatic sites. Follow-up evaluation using MDP is limited since one infrequently discovers new abnormal MDP uptake without corresponding MIBG uptake. Moreover, this kind of abnormalities are highly unspecific and may correspond to any lesion not related to neuroblastoma.

III Common Indications

Indications

A. Confirmation in suspected neuroectodermally derived tumours including neuroblastoma, phaeochromocytoma and ganglioneuroma.
B. Staging of the disease.
C. Follow-up of neuroblastoma under chemotherapy, particularly in stage IV and IVs patients.
D. Before and after surgery of the primary tumour.
E. Follow-up after treatment to exclude a sub-clinical relapse, especially in the bone marrow and also in the case of any clinical abnormality during follow-up, particularly bone pain.
F. Before planning MIBG therapy

Contra Indications

There are no contra indications.

IV Procedure

Referring physicians should be informed that radioiodinated MIBG is a cyclotron product and therefore not continuously available at all times. Several days are required to obtain the MIBG also there is a period (days) between injection and scan depending on which iodine nuclide is used.

A. Information about previous examinations relevant to this procedure

The clinical information related to the patient, the reason for performing the examination, the biochemical data, the previous treatment (i.e. surgery, chemo- and/or radiotherapy) and diagnostic procedures should be available.

B. Patient Preparation

B.1 Information with appointment letter:

Child and parents should receive detailed information about the entire procedure. The thyroid should be blocked (see § B.2). Ensure that the actions (see § C. Precautions) prior to the injection of tracer have been carefully explained to the family or to ward staff for in-patients. This will require a special information sheet. Good hydration is advocated to lower the radiation burden.

Prior to Injection: On arrival in the department a local anaesthetic cream can be used; it should be applied at least 60 minutes before the injection.

B.2 Thyroid blockade

Thyroid blockade is important to protect the thyroid from unnecessary irradiation, an organ that is more radiosensitive in children than in adults.

Beginning on the day before tracer injections until the day after injection, children from one month to three years should receive 32 mg potassium iodide daily, from three to thirteen years 65 mg, and over this age 130 mg daily. New-borns receive 16 mg potassium iodide only on the day before tracer injection.

Rapid blockade by perchlorate (Irenat) is an alternative option.

B.3 Drugs interactions

Many classes of medicines interfere with MIBG uptake and storage [21]. Treatment prescribed before and at the time of MIBG injection and imaging procedure should always be checked with the referring physician. Unlike in adult patients, the list of usually concerned substances is actually limited.

The most common are bronchodilators containing: Fenoterol (Berotec ®), Salbutamol (Ventolin®), Terbutaline (Bricanyl®) and nasal drops and sprays containing Xylometazoline (Otrivine drops®).

The possibility of over the counter medicines should also be kept in mind.

Many cardiac drugs interfere with MIBG and although such drugs are rarely found in a paediatric population, special attention should be paid to cases of suspected phaeochromocytoma. Those usually prescribed in children are:

- Calcium channel blockers: Nifedipine (Adalat®), Nicardipine (Cardene®), Amlodipine (Norvasc®),
- Angiotensin-Converting Enzyme inhibitors: Captopril (Capoten®), Enalapril (Vasotec®),
- Adrenergic Receptor Blockers: Labetalol (Trandate®), Amiodarone (Cordarone®),
- Inhibition of sodium pump: Digoxin (Lanoxin®).

C. Precautions

1. Check if thyroid blockade has been given .
2. Check on going treatment for possible drugs interactions.
3. The tracer must be injected slowly, preferably over a period up to 5 minutes.

D. Radiopharmaceutical

D.1 Radionuclide

- Iodo-123 (^{123}I)
- Iodo-131 (^{131}I)

D.2 Pharmaceutical

- MIBG (Meta-iodobenzylguanidine)

^{123}I-MIBG is the radiopharmaceutical of choice in children giving high quality images. Gamma emission energy of 159 keV for ^{123}I is more suitable for imaging than 360 keV for ^{131}I and the differences in terms of radiation burden permit to inject higher activities with ^{123}I compared to ^{131}I. Result of ^{123}I-MIBG scintigraphy is also more rapidly available for the clinician.

^{131}I-MIBG that is more widely available, is an acceptable second choice and may be preferred when

estimation of the tumour's MIBG-retention is required for therapy planning.

D.3 Dose Schedule (see § **V Issues requiring further clarification**).

Minimum doses: ^{123}I-MIBG = 80 MBq
^{131}I -MIBG = 35 MBq

Recommended maximum doses: ^{123}I-MIBG = 400 MBq
^{131}I -MIBG = 80 MBq

Administered doses should be scaled down to body weight[22] .

D.4 Injection technique

Slow injection (at least 5 min) in peripheral vein, flushed with saline. Potential adverse effects of MIBG (vomiting, tachycardia, pallor, abdominal pain) that are not related to allergy are very rare in case of slow injection. Rapid injection is contraindicated as it causes the above adverse effects. Injection via central venous catheters should be avoided if possible and in that case injection should be even slower.

D.5 Radiation Burden

Depending on administered activity and on the child's age. i.e.: 3,7mSv for a 5 year old child receiving 5.18MBq/kg 123I-MIBG [23] and 5.5mSv for a for a 5 year old child receiving 0.74 MBq/kg ^{131}I-MIBG [23]

E. Image Acquisition

An adapted environment, an adequate attitude toward the child, a well-trained technologist for paediatric procedures and involved parents before and during the procedure all help in obtaining a co-operative child.

Sedation is usually not required for a technical satisfactory examination. The most difficult age is between 1 and 3 years. In this category, sedation might be necessary [24].

E.1 Timing for imaging

Using ^{123}I -MIBG images are acquired 20-24 hours after the injection.

Selected delayed images - never later than 48h - may be useful in the odd cases with equivocal findings.

Using ^{131}I-MIBG, scanning is generally performed 48h after the injection and can be repeated at day 3 or later.

E.2 Collimator

Use the collimator suitable respectively for ^{123}I and ^{131}I energy depending on manufacturer’s recommendations.

E.3 Positioning of the child

The highest quality images are obtained by having the child as close as possible to the camera face, if possible on the camera face. A special table - if available - with an aperture for the collimator will allow imaging of the patient lying directly on the collimator.

E.4 Views

Whole body scan imaging with additional spot images including lateral views of the skull, can be considered especially in children able to lie still for the entire acquisition time. However spot images of the entire body are the reference method.

- Skull anterior, posterior
- Skull right, left (including arms)
- Chest anterior, posterior
- Abdomen anterior, posterior
- Pelvis (empty bladder) anterior, posterior (lateral if bladder is not empty)
- Lower limbs anterior, posterior

These views should be similar to those obtained with bone scans i.e. the toes turned inwards and the knees together. The ankles should be included.

E.5 Computer acquisition set up

Static images: 250.000 counts or 10 min counting per image are necessary (compromise between best image quality and limitation of scanning time). A pixel size of approximately 2 mm requires a 256x256 matrix or 128x128 matrix with zoom.

Whole body scanning: a scan speed of 5 cm/min or a total acquisition time of 30 minutes is appropriate.

E.6 Optional images

Landmarking: In certain circumstances, it can be of help to use other tracers in conjunction with MIBG. In case of difficulties to differentiate between MIBG tumour uptake and retention of activity in the renal pelvis one may either use furosemide to washout the pelvic activity or use MAG3/DTPA to identify the kidney. A bladder catheter is not necessary except in particular cases. However, even in pelvic neuroblastoma, the bladder activity is rarely a problem. The child (if co-operative) should be encouraged to void prior to the imaging.

SPECT imaging: In cases where uncertainty exists as to the exact site of MIBG activity SPECT may be useful. The abdomen is the area where this is most likely to occur: lesions in or close to the liver, as well as close to the bladder or any other area of intense physiological uptake are particularly good indications to add SPECT. The feasibility of SPECT will depend on the child and on the equipment available (multiple head camera) [25-27].

F. Intervention: not relevant.

G. Processing: not relevant.

H. Hard Copy Output

Grey scale of all images that have been acquired.

I. Interpretation/ Reporting/ Pitfalls

I.1 Normal biodistribution

Knowledge of normal biodistribution is necessary to avoid misinterpretations[28-30]. MIBG is normally taken

up by liver, spleen, myocardium, salivary glands and normal adrenals. The myocardial uptake may be particularly high, especially in children under 1 year. In the other cases, there is a balance between liver and myocardial uptake. Skeletal muscles, nasal mucosa, lungs, urinary tract, colon, gallbladder and thyroid may also demonstrate accumulation of tracer of variable intensity. Uptake of MIBG by the various organ systems reflects either rich adrenergic innervation or catecholamine excretion (or both) [2, 28].

Free iodine causes thyroid uptake (which can be blocked with stable iodine or perchlorate (see § B.2)) and some digestive artefacts[29].

No skeletal uptake should be seen. Extremities show only slight muscular activity and in these cases the bone may appear as a photon deficient area (as observed at the level of the knees).

I.2 Pathology

MIBG soft tissue uptake is observed in the primary tumour and in metastatic sites including lymph nodes, liver, bone and bone marrow.

Intensity of MIBG uptake can be similar in benign and malignant tumours. Similarly, maturation of neuroblastoma may occur with no change in intensity of uptake.

MIBG skeletal uptake can be observed either as focal areas of increased uptake or as a diffuse skeletal uptake. The increase of tracer uptake is related either to bone metastases or to bone marrow infiltration or both.

I.3 False negative scans

One or several lesions could be missed due to a variety of reasons:

a) physical reasons related to limited spatial resolution which will prevent detection of small lesions,
b) anatomical reasons, with lesions located close to a voluminous primary or metastatic mass, or close to soft tissue with a high physiological uptake (myocardium, thyroid and salivary glands, liver, kidney, bladder and colon)[14, 29],
c) no tumour uptake or low tumour uptake related to physiopathological reasons arising from tumour heterogeneity, ischaemic necrosis in the tumour mass, lack of granules, loss of tumour capacity to take up the tracer, pharmaceutical inhibition or unknown reason [12].

J. Quality control

Due to the long acquisition time, it is important to check for movement in each image recorded. This has to be done before the child leaves the department.

V Issues requiring further clarification

The amount of activity to be injected, reported in D.3 is higher than that proposed by EANM paediatrics task group[22]. There is actually no scientific basis to suggest that there is a “correct” amount of radiotracer to inject. Accurate staging is a priority and experience gained from MIBG therapy has learned us that sensitivity of detection with MIBG increases with increased activity injected.

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