Eur J Nucl Med Mol Imaging (2008) 35:1039–1047
DOI 10.1007/s00259-008-0715-3

GUIDELINES

EANM procedure guidelines for ^{131}I-meta-iodobenzylguanidine (^{131}I-mIBG) therapy

Francesco Giammarile · Arturo Chiti · Michael Lassmann · Boudewijn Brans · Glenn Flux

Published online: 15 February 2008

Abstract Meta-iodobenzylguanidine, or Iobenguane, is an aralkylguanidine resulting from the combination of the benzyl group of bretylium and the guanidine group of guanethidine (an adrenergic neurone blocker). It is a noradrenaline (norepinephrine) analogue and so-called "false" neurotransmitter. This radiopharmaceutical, labeled with ^{131}I, could be used as a radiotherapeutic metabolic agent in neuroectodermal tumours, that are derived from the primitive neural crest which develops to form the sympathetic nervous system. The neuroendocrine system is derived from a family of cells originating in the neural crest, characterized by an ability to incorporate amine precursors with subsequent decarboxylation. The purpose of this guideline is to assist nuclear medicine practitioners to evaluate patients who might be candidates for ^{131}I-meta-iodobenzylguanidine to treat neuro-ectodermal tumours, to provide information for performing this treatment and to understand and evaluate the consequences of therapy.

Keywords Guidelines · Therapy · mIBG

F. Giammarile (✉)
CH Lyon Sud, EA 3738, HCL, UCBL,
165 Chemin du Grand Revoyet,
69495 Pierre Benite Cedex, France
e-mail: francesco.giammarile@chu-lyon.fr

A. Chiti
U.O. di Medicina Nucleare, Istituto Clinico Humanitas,
via Manzoni, 56,
20089 Rozzano (MI), Italy
e-mail: arturo.chiti@humanitas.it

M. Lassmann
Klinik und Poliklinik für Nuklearmedizin,
Universität Würzburg,
Josef-Schneider-Str. 2,
97080 Würzburg, Germany
e-mail: Lassmann_M@klinik.uni-wuerzburg.de

B. Brans
Department of Nuclear Medicine,
University Medical Center Maastricht,
P. Debyelaan 25, Postbox 5800,
6202 AZ Maastricht,
The Netherlands
e-mail: b.brans@lnug.azm.nl

G. Flux
Royal Marsden Hospital, Downs Road, Sutton,
Surrey SM2 5PT, UK
e-mail: glenn.flux@icr.ac.uk

Purpose

The purpose of this guideline is to assist nuclear medicine practitioners to

1. Evaluate patients who might be candidates for ^{131}I-meta-iodobenzylguanidine (mIBG) to treat neuro-ectodermal tumours
2. Provide information for performing this treatment
3. Understand and evaluate the consequences of therapy

Background information and definitions

Definitions

The following are the definitions in this guideline:

1. ^{131}I is a beta-emitting radionuclide with a physical half-life of 8.04 days, a principal gamma ray of 364 KeV (81% abundance) and beta particles with a maximum energy of 0.61 MeV and an average energy of 0.192 Mev.
2. mIBG or Iobenguane is an aralkylguanidine resulting from the combination of the benzyl group of bretylium

and the guanidine group of guanethidine (an adrenergic neurone blocker). It is a noradrenaline (norepinephrine) analogue and a so-called false neurotransmitter.
3. The neuroendocrine system is derived from a family of cells originating in the neural crest and is characterised by an ability to incorporate amine precursors with subsequent decarboxylation.
4. Neuroectodermal tumours derive from the primitive neural crest, which develops to form the sympathetic nervous system.
5. Therapy in this context means the intravenous infusion of ^{131}I-mIBG.
6. Malignant neuroectodermal tumours in this context include phaeochromocytoma, paraganglioma, carcinoid tumours, medullary thyroid cancer and neuroblastoma.

Background

Because of the structural similarity with noradrenaline, after intravenous injection, 131I-mIBG is selectively concentrated by tissues with rich adrenergic innervation, essentially neuroectodermal tissue, including tumours of neuroectodermal origin. mIBG may be taken into cells by either the neuronal uptake-1 mechanism or by passive diffusion and stored in neurosecretory granules (in neuroblastoma, neurosecretory granules are thought to play a minor role and a fast re-uptake after passive outward diffusion is suggested). The transfer of mIBG from intracellular cytoplasm into catecholamine storage vesicles (neurosecretory vesicles) is mediated by an ATPase-dependent proton pump. Unlike noradrenaline, mIBG is not metabolised and is excreted unchanged [1].

The presumed mechanism of action is the emission of ionising radiation from the decaying radionuclide 131I. Ninety percent of the radiation effects result from the beta radiation, which has a mean range in tissue of about 0.5 mm [2–6].

Indications

The indications are tumours showing adequate uptake and retention of radiolabelled mIBG on the basis of a pre-therapy tracer study. Because there is no clear agreement on what should be considered adequate uptake, the final decision must be based on imaging and clinical considerations:

1. Inoperable phaeochromocytoma
2. Inoperable paraganglioma
3. Inoperable carcinoid tumour
4. Stage III or IV neuroblastoma
5. Metastatic or recurrent medullary thyroid cancer

Contra-indications

Absolute

The following are absolute contra-indications:

1. Pregnancy; breastfeeding
2. Life expectancy less than 3 months, unless in case of intractable bone pain
3. Renal insufficiency, requiring dialysis on short term

Relative

The following are relative contra-indications:

1. Unacceptable medical risk for isolation
2. Unmanageable urinary incontinence
3. Rapidly deteriorating renal function—glomerular filtration rate less than 30 ml/min
4. Progressive haematological and/or renal toxicity because of prior treatment
5. Myelosuppression:
   - Total white cell count less than 3.0×10^9/l
   - Platelets less than 100×10^9/l

In case of low white blood cell counts, low platelet counts, massive bone marrow invasion and/or impaired renal function, the administered activity should be reduced, and close follow-up is recommended to anticipate toxicity.

Procedure

Facility and personnel

The facilities requirements will depend on national legislation on the therapeutic use of radioactive-emitting agents. Most of the time, in-patient treatment is required by national legislation; therefore, this should take place in an approved facility with appropriately shielded rooms and en-suite bathroom facilities.

The facility in which treatment is administered must have appropriate personnel, radiation safety equipment, procedures available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread.

The administration of ^{131}I should be undertaken by appropriately trained medical staff with supporting nursing staff and available medical physics expert (according to European directive EURATOM 97/43) [7].

Physicians responsible for treating patients should have an understanding of the clinical pathophysiology and natural history of the disease processes, should be familiar with

other forms of therapy, and should be able to liaise closely with other physicians involved in managing the patient.

Children undergoing ^{131}I-mIBG therapy should be managed jointly by teams including the specialist paediatric staff [8].

Clinicians involved in unsealed source therapy must be knowledgeable about and compliant with all applicable national and local legislation and regulations.

Patient preparation and data required

1. Patients should have a proven, inoperable neuro-endocrine tumour and have undergone conventional staging investigations including mIBG scintigraphy, anatomical imaging (CT, MRI, ultrasound) and biochemical assessment to identify objective tumour markers.
2. Eligible patients will have mIBG-positive tumours, documented by tracer scintigraphy using ^{123}I-mIBG as a diagnostic tracer (in adults, ^{131}I-mIBG can also be used for tumour imaging).
3. Thyroidal uptake of free iodide is prevented using per oral stable iodine (Table 1) Capsules of oral iodine are more suitable for children because of their neutral taste. The treatment should begin 48–24 h before the planned mIBG administration and continued for 10–15 days post-therapy. Potassium perchlorate, normally used alone before mIBG scintigraphy, is here generally used in combination with stable iodine to facilitate the wash-out of the radio-iodine from the thyroid. Hormonal treatment with *thyroxine* or *neomercazole* is generally not indicated.
4. Many classes of medicines may theoretically interfere with mIBG uptake and storage (Table 2) [9]. Ideally, drugs likely to interfere with the uptake and/or retention of mIBG should be withdrawn before treatment, and patients should be stabilised on alternative medication. However, patients with metabolically active catecholamine-secreting tumours (i.e. phaeochromoctyoma, paraganglioma) are often alpha and beta blocked by medical treatment, before mIBG. A considerable number of such patients with catecholamine-secreting tumours are at risk to develop symptoms after withdrawal of their medication. Furthermore, hypertension induced by mIBG is always possible, even if rare in children [10]. Therefore, we recommend that in these patients, the diagnostic scintigraphy and the therapeutic administration of mIBG are conducted without changing the medication taken, although using beta blockers or calcium channels blockers could impair the efficacy of procedure. In the other patients, a slow administration of the mIBG, which should be stopped if hypertension occurs, is recommended (see "Administration").

Patient information and instruction

Patients should receive both written and verbal information about the procedure before receiving therapy. If necessary, informed written consent must be obtained from the patient [11].

After appropriate guidance, comforters and carers may be encouraged to participate in the care of children undergoing mIBG therapy, especially in case of small children, depending on local regulations. Usually these carers will be family members, i.e. parents and/or grandparents. If these carers are expected to receive a radiation burden exceeding the constraints of 1 mSv/year, an informed consent should be obtained in accordance with the status of 'willingly and knowingly exposed comforters and carers,' and an annual constraint should be defined. This may be for instance the maximum tolerated dose for exposed workers or 5 mSv/year, depending on national regulations. The fact that treatment sessions are often performed several times a year should be taken in account for assessment of the acceptable radiation burden for the relatives. Female carers willingly and knowingly exposed should be advised to take appropriate contraception and should not be breastfeeding.

Carers of patients who have received mIBG should receive specific instructions with regard to radiation safety precautions. Radiation protection rules on reducing unnecessary radiation exposure to family members and the public should be clearly explained to the patients and the relatives. Written instructions should be provided where required.

Table 1 Thyroid blockade

Compound	Adults	Children (15–50 kg)	Children (5–15 kg)	Children (<5 kg)
Capsules	mg/daily			
Potassium iodate	170	80	40	20
Potassium iodide (KI)	130	65	32	16
Lugol solution 1%	1 drop/kg per day with a maximum of 40 (20 drops twice daily)			
Capsules	mg/daily			
Potassium perchlorate	400	300	200	100

Table 2 Drugs interactions with ^{131}I-mIBG

Drug group	Approved name	Recommended withdrawal time	Mechanism of interaction[a]
Cardiovascular and sympathomimetic drugs			
Anti-arrhythmics for ventricular arrhythmias	Amiodarone	Not practical to withdraw	**1, 3**
Combined alpha and beta blocker	Labetalol	72 h	**1, 3**
Adrenergic neurone blockers	Brethylium	48 h	*2*, *3*
	Guanethidine	48 h	*2*, *3*
	Reserpine	48 h	2, 3
Alfa blockers	Phenoxybenzamine (IV doses only)	15 days	**5**
Calcium channel blockers	Amlodipine	48 h	*4*, *5*
	Diltiazem	24 h	4, 5
	Felodipine	48 h	*4*, *5*
	Isradipine	48 h	*4*, *5*
	Lacidipine	48 h	*4*, *5*
	Lercanidipine	48 h	*4*, *5*
	Nicardipine	48 h	4, 5
	Nifedipine	24 h	4, 5
	Nimodipine	24 h	4, 5
	Nisoldipine	48 h	*4*, *5*
	Verapamil	48 h	**4, 5**
Inotropic sympatho-mimetics	Dobutamine	24 h	*3*
	Dopamine	24 h	*3*
	Dopexamine	24 h	*3*
Vasoconstrictor sympathomimetics	Ephedrine	24 h	1
	Metaraminol	24 h	3
	Norepinephrine	24 h	3
	Phenylephrine	24 h	3
$Beta_2$ stimulants (sympathomimetics)	Salbutamol	24 h	*3*
	Terbutaline	24 h	*3*
	Eformoterol	24 h	*3*
	Bambuterol	24 h	*3*
	Fenoterol	24 h	*3*
	Salmeterol	24 h	*3*
Other adrenoreceptor stimulants	Orciprenaline	24 h	*3*
Systemic and local nasal decongestants, compound cough and cold preparations	Pseudoephedrine	48 h	**3**
	Phenylephrine	48 h	**3**
	Ephedrine	24 h	**1**
	Xylometazoline	24 h	**3**
	Oxymetazoline	24 h	**3**
Sympathomimetics for glaucoma	Brimonidine	48 h	*3*
	Dipivefrine	48 h	*3*
Neurological drugs			
Antipsychotics (neuroleptics)	Chlorpromazine	24 h	*1*
	Benperidol	48 h	*1*
	Flupentixol	48 h or 1 month for depot	*1*
	Fluphenazine	24 h or 1 month for depot	*1*
	Haloperidol	48 h or 1 month for depot	*1*
	Levomepromazine	72 h	*1*
	Pericyazine	48 h	*1*
	Perphenazine	24 h	*1*
	Pimozide	72 h	*1*
	Pipotiazine	1 month for depot	*1*
	Prochlorperazine	24 h	*1*
	Promazine	24 h	*1*
	Sulpiride	48 h	*1*
	Thioridazine	24 h	*1*
	Trifluoperazine	48 h	*1*

Table 2 (continued)

Drug group	Approved name	Recommended withdrawal time	Mechanism of interaction[a]
	Zuclopenthixol	48 h or 1 month for depot	*1*
	Amisulpride	72 h	*1*
	Clozapine	7 days	*1*
	Olanzapine	7–10 days	*1*
	Quetiapine	48 h	*1*
	Risperidone	5 days or 1 month for depot	*1*
	Sertindole	15 days	*1*
	Zotepine	5 days	*1*
Sedating antihistamines	Promethazine	24 h	*1*
Opioid analgesics	Tramadol	24 h	**1**
Tricyclic anti-depressants	Amitriptyline	48 h	**1**
	Amoxapine	48 h	1
	Clomipramine	24 h	**1**
	Dosulepin (Dothiepin)	24 h	**1**
	Doxepin	24 h	1
	Imipramine	24 h	**1**
	Lofepramine	48 h	**1**
	Nortriptyline	24 h	1
	Trimipramine	48 h	**1**
Tricyclic-related anti-depressants	Maprotiline	48 h	*1*
	Mianserin	48 h	*1*
	Trazolone	48 h	*1*
	Venlaflaxine	48 h	*1*
	Mirtazepine	8 days	*1*
	Reboxetine	3 days	*1*
CNS Stimulants	Amphetamines, e.g. Dexamfetamine	48 h	*3*
	Atomoxetine	5 days	*1*
	Methylphenidate	48 h	*5*
	Modafinil	72 h	*5*
	Cocaine	24 h	**1**
	Caffeine	24 h	*5*

[a] Mechanisms of interaction
1 Inhibition of sodium-dependent uptake system i.e. uptake—one inhibition, *2* transport interference—inhibition of uptake by active transport into vesicles, i.e. inhibition of granular uptake, and competition for transport into vesicles, i.e. competition for granular uptake, *3* depletion of content from storage vesicles/granules, *4* calcium mediated, *5* other, possible, unknown mechanisms (adapted from the Radiopharmacy Protocol of the Nuclear Medicine Department, Queen Elizabeth Hospital, Birmingham, UK). Theoretical mechanism of interaction in italic, high significance mechanism of interaction in bold, probable mechanism of interaction in standard

When children are in isolated hospitalisation, parents or other adult relatives should be strongly encouraged to be involved in the child's care. They need to be instructed to restrict the time of exposure, to keep as much distance as possible and to avoid drinking or eating in the isolation room. They must be trained to use appropriate protective clothing. The external radiation dose to the parents can be monitored continuously by a pocket dosimeter, and internal contamination can be evaluated, if necessary, by measuring a urine sample in a gammacounter.

Administration

^{131}I-mIBG, diluted in compliance with the manufacturer's instructions, is administered by slow intravenous infusion (45 min to 4 h) via an indwelling cannula or central venous line using a lead-shielded infusion system. The infusion line should be flushed at the same rate at the end of the procedure.

Monitoring of vital signs is essential as mIBG administration may result in unstable blood pressure. Vital signs should be checked before and after the infusion and at least twice daily afterwards. More frequent monitoring is recommended in the case of catecholamine-secreting tumours. Short-acting alpha or beta blockers should be available for emergency use in the event of catecholamine surge during or immediately after ^{131}I-mIBG administration. In practice, unstable hypertension can be managed by reducing or temporarily stopping the ^{131}I-mIBG infusion. In some cases, additional alpha or beta blockers are essential.

Prophylactic anti-emetics are advised, commencing on the day of treatment, continued for 72 h. To avoid possible drug interaction, *Ondansetron* is the anti-emetic of choice. During this period, patients should also be encouraged to drink some extra fluids, to limit the extra-tumoural radiation burden, especially to the bladder.

Usual single-administered activities range between 3.7 (100 mCi) and 11.2 GBq (300 mCi). The administered activity may be modified for medical reasons such as tumour burden or according to local legislation. Because several therapeutic doses may be required to achieve objective response, these activities are often repeated at widely different intervals. Activity reduction should be considered in patients with myelosuppression and impaired renal function. Further, much higher activities may be administered if administration is given according to, e.g. a whole-body absorbed dose. In ^{131}I-mIBG therapy, the bone marrow is the dose-limiting organ. In a cohort of patients with neuroblastoma who had received prior intensive chemotherapy, it has been shown that the dose-limiting toxicity of single-fraction ^{131}I-mIBG is myelotoxicity at 2-Gy whole-body dose, according to pre-therapeutic ^{131}I-mIBG scans. This is circumvented if bone marrow stem cell support is available. A total of 4.0 Gy whole-body dose with stem cell rescue has been given with good tolerance and no other short-term, dose-limiting organ toxicity [2, 13, 14].

Precautions, follow-up and side effects

Nursing personnel must be instructed in radiation safety. Any significant medical conditions should be noted and contingency plans made in case radiation precautions must be breached for a medical emergency. Concern about radiation exposure should not interfere with the prompt appropriate medical treatment of the patient.

Urinary ^{131}I-mIBG excretion is of particular concern during the first 5 days post-administration. Patients should be advised to observe rigorous hygiene to avoid contaminating persons using the same toilet facility. Patients should be warned to avoid soiling underclothing or areas around toilet bowls for 1 week post-injection. Significantly soiled clothing should be washed separately. A double toilet flush is recommended after urination. Patients should wash their hands after urination.

Incontinent patients should be catheterised before ^{131}I-mIBG administration. The catheter should remain in place for 3 to 4 days. Catheter bags should be emptied frequently. Gloves should be worn by staff caring for catheterised patients (or for any procedure involving contact).

Haematological monitoring is essential post-therapy to anticipate significant myelosuppression and to plan subsequent treatment cycles. Quantitative post-therapy scintigraphy may be of value to clarify tumour extent and perform dosimetry calculations.

After treatment, patients should avoid pregnancy for at least 4 months. Male patients should consider sperm banking before therapy.

Side effects

Early The following are early side effects:

1. Temporary nausea and vomiting may occur during the first 2 days after administration
2. Temporary myelosupression which typically occurs 4–6 weeks post-therapy. Haematological effects are common in children with neuroblastoma after chemotherapy (60%), predominantly as an isolated thrombocytopenia, but are less frequent in adults
   a. Bone marrow depression is likely in patients who have bone marrow involvement at the time of ^{131}I-mIBG therapy and, because of a high whole-body radiation dose, in patients with delayed renal ^{131}I-mIBG clearance.
   b. ^{131}I-mIBG therapy is associated with significantly less haematological toxicity in chemotherapy naïve patients.
3. Rarely, deterioration of renal function is observed in patients whose kidneys have been compromised by intensive pretreatment with cisplatin and ifosfamide
4. Rarely, in adults with phaeochromocytoma or paraganglioma and children with neuroblastoma, hypertensive crises may be evoked by release of catecholamines, requiring alpha blockade. In patients with carcinoid, flushing may occur because of release of serotonin

Late Possible long-term effects are those known of ^{131}I therapy in general, such as:

1. Hypothyroidism (after inadequate thyroid blockade)
2. Persistent haematological effects (thrombocytopaenia, myelosuppression)
3. There is sparse evidence for induction of leukaemia or secondary solid tumours, but this is a rare possibility, especially in conjunction with (longstanding) chemotherapy treatment [15]

Radiopharmaceutical

Approved name The approved name of the radiopharmaceutical is Iodine [^{131}I] meta-iodobenzylguanidine (^{131}I-mIBG).

High specific activity (up to 1.48 GBq/mg) is recommended for therapy use. The radionuclide is supplied frozen in aqueous solution or in glucose solution.

It is essential that the manufacturer's instructions are adhered to prevent deterioration of the product. Impurities (e.g. free ^{131}I) will not contribute to tumour targeting but may contribute to the side effects of the treatment.

Where necessary, defrosting is achieved by placing the vial within its lead container in a less than 50°C water bath for 45 min.

A sample is withdrawn for quality control of radionuclide and radiochemical purity.

Labelling For therapy purposes, mIBG is labelled with [^{131}I] iodine (^{131}I-mIBG).

Dosimetry According to the European directive EURATOM 97/43, absorbed dose estimates should be obtained in all cases. In accordance with national regulations, a medical physicist, preferably experienced in in vivo dosimetry, should perform the dosimetry calculations [7].

1. Pre-therapeutic dosimetry scanning can be used clinically to determine the predicted level of uptake and retention from a therapeutic administration and thus predict the individual degree of bone marrow toxicity, on the basis of a previously observed dose–toxicity relationship between bone marrow suppression and the whole-body radiation dose, which can thus be used as a surrogate for bone marrow radiation dose [16–18].
2. Tumour-absorbed doses vary widely and so provide useful information regarding treatment efficacy [12, 19, 20].

Whilst dosimetry methodology varies widely, the following parameters should be reported to allow a standardisation between therapies, patients and institutions:

Whole-body dosimetry

1. Method of obtaining measurement: a ceiling-mounted geiger counter is recommended [21], although a hand-held counter is an acceptable substitute if sufficient care is taken
2. Number of measurements acquired
3. Method of integration
4. The *S* value used (assuming that MIRD methodology is followed) [22]

Tumour/normal organ dosimetry

1. Method of scanning
2. Times of scans
3. Scatter correction techniques (if any)
4. Attenuation corrections (if any)
5. Method to determine the volume of interest
6. Method of image reconstruction (in the case of SPECT)

It should be noted that the absorbed doses given in the Table 3 were derived from a diagnostic administered activities. Therefore, the absorbed doses per unit administered activity given in this guideline should not be applied to practical dosimetry for an individual patient in a therapeutic setting and should also not be used prospectively for the prediction of the treatment-related toxicity in an individual patient.

Besides, the above data are valid in normal pharmacokinetic behaviour. When renal function is impaired because of disease or previous therapy, the radiation dose delivered to organs (notably to bone, red marrow and lungs) might be increased considerably.

Table 3 Lists of organs with the highest radiation absorbed dose

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	Children			
		15 years	10 years	5 years	1 year
Bone surfaces	6.1E−02	7.2E−02	1.1E−01	1.8E−01	3.6E−01
Breast	6.9E−02	6.9E−02	1.1E−01	1.8E−01	3.5E−01
Kidneys	1.2E−01	1.4E−01	2.1E−01	3.0E−01	5.1E−01
Lungs	1.9E−01	2.8E−01	3.9E−01	6.0E−01	1.2E+00
Gonads					
Ovaries	6.6E−02	8.8E−02	1.4E−01	2.3E−01	4.2E−01
Testes	5.9E−02	7.0E−02	1.1E−01	1.9E−01	3.6E−01
Red marrow	6.7E−02	8.3E−02	1.3E−01	1.9E−01	3.5E−01
Thyroid	5.0E−02	6.5E−02	1.1E−01	1.8E−01	3.5E−01
Adrenals	1.7E−01	2.3E−01	3.3E−01	4.5E−01	6.9E−01
Bladder wall	5.9E−01	7.3E−01	1.1E+00	1.7E+00	3.3E+00
Liver	8.3E−01	1.1E−00	1.6E+00	2.4E+00	4.6E+00
Salivary glands	2.3E−01	2.8E−01	3.8E−01	5.1E−01	7.5E−01
Spleen	4.9E−01	6.9E−01	1.1E+00	1.7E+00	3.2E+00
Uterus	8.0E−02	1.0E−01	1.6E−01	2.6E−01	4.8E−01

The "effective dose equivalent" (EDE) is no longer in use; it has been replaced by the "effective dose" (ED). The ED reflects the stochastic risk of radiation and may be inappropriate for the assessment of the risk associated with non-stochastic radiation effects in targeted radionuclide therapy. The previously used EDE in an adult was 0.2 mSv/MBq (mentioned in ICRP 53 [23]). The ED in an adult is 0.14 mSv/MBq (mentioned in ICRP 60 [24]).

Quality control The amount of activity to be administered should be checked using an isotope calibrator.

Issues requiring further clarification

The following are issues requiring further clarification:

1. mIBG treatment
   - 1.1 Optimal administered activity per treatment cycle
   - 1.2 Total number of treatments and treatment interval by tumour type
   - 1.3 Role of ^{131} I-mIBG in neuroblastoma:
     - 1.3.1 In first line treatment
     - 1.3.2 In multimodality treatment (e.g. combined with topotecan and/or bone marrow ablative therapy with stem cells rescue)
2. Dosimetry
   - 2.1. Relation with toxicity and response
   - 2.2. Optimisation of the methodology to calculate whole body and tumour dosimetry
   - 2.3. Need for randomised clinical trials

References

1. Wafelman AR, et al. Radio-iodinated MIBG: a review of its biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry. Eur J Nucl Med 1994;21:545–59.
2. Weiland DM, Wu J, Brown LE, Manger TJ, Swanson DP, Beierwaltes WH. Radiolabeled adrenergic neuron-blocking agents: adrenomedullary imaging with 131I meta-iodobenzylguanidine. J Nucl Med 1980;21:349–53.
3. Beierwaltes WH. Treatment of neuroblastoma with 131I-MIBG: dosimetric problems and perspectives. Med Pediatr Oncol 1987;15:188–91.
4. Giammarile F, Lumbroso J, Ricard M, Aubert B, Hartmann O, et al. Radioiodinated metaiodobenzylguanidine in neuroblastoma: influence of high dose on tumour site detection. Eur J Nucl Med 1995;22(10):1180–3 (Oct).
5. Hoefnagel CA, Lewington VJ. MIBG therapy. In: Murray IPC, Ell PJ, editors. Nuclear medicine in clinical diagnosis and treatment. vol 2. 2nd ed. New York: Churchill Livingstone; 1998. p. 1067–81.
6. Garaventa A, Gambini C, Villavecchia G, et al. Second malignancies in children with neuroblastoma after combined treatment with 131I-MIBG. Cancer 2003;97(5):1332–8 (Mar 1).
7. Radiation Protection, European Commission. Radiation protection following iodine-131 therapy (Exposures due to outpatients or discharged inpatients). Radiation Protection 97.
8. Schmidt M, Simon T, Hero B, Eschner W, Dietlein M, Sudbrock F, et al. Is there a benefit of I-131-MIBG therapy FOR in the treatment of children with stage 4 neuroblastoma? Nuklearmedizin 2006;45(4):145–51.
9. Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). Nucl Med Commun 1992;13:513–21.
10. Matthay KK, Yanik G, Messina J, Quach A, Huberty J, Cheng SC, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. J Clin Oncol 2007;25(9):1054–60 Mar 20.
11. Royal HD, Pierson JR, Fletcher JW, et al. Procedure guideline for guideline development. J Nucl Med 1996;37:878–81.
12. Lashford LS, Lewis IJ, Fielding SL, Flower MA, Meller ST, Kemshead JT, et al. Phase I/II study of iodine-131 metaiodobenzylguanidine in chemoresistant neuroblastoma: a United Kingdom Children's Cancer Study Group investigation. J Clin Oncol 1992;10:1889–96.
13. Matthay KK, Panina C, Huberty J, Price D, Glidden DV, Tang HR, et al. Correlation of tumour and whole-body dosimetry with tumour response and toxicity in refractory neuroblastoma treated with (131)I-MIBG. J Nucl Med 2001;42(11):1713–21. Nov.
14. Gaze MN, Chang YC, Flux GD, Mairs RJ, Saran FH, Meller ST. Feasibility of dosimetry-based high-dose I-131-meta-iodobenzylguanidine with topotecan as a radiosensitizer in children with metastatic neuroblastoma. Cancer Biother Radiopharm 2005;20(2):195–9.
15. Weiss B, Vora A, Huberty J, Hawkins RA, Matthay KK. Secondary myelodysplastic syndrome and leukemia following 131I-MIBG therapy for relapsed neuroblastoma. J Pediatr Hematol Oncol 2003;25(7):543–7 (Jul).
16. Monsieurs MA, Thierens HM, Vral A, Brans B, De Ridder L, Dierckx RA. Patient dosimetry after I-131-MIBG therapy for neuroblastoma and carcinoid tumours. Nucl Med Commun 2001;22(4):367–74.

17. Flux GD, Guy MJ, Beddows R, Pryor M, Flower MA. Estimation and implications of random errors in whole-body dosimetry for targeted radionuclide therapy. Phys Med Biol 2002;47(17):3211–23.
18. Flux GD, Guy MJ, Papavasileiou P, South C, Chittenden SJ, Flower MA, et al. Absorbed dose ratios for repeated therapy of neuroblastoma with I-131 mIBG. Cancer Biother Radiopharm 2003;18(1):81–7.
19. Fielding SL, Flower MA, et al. Dosimetry of iodine 131 metaiodobenzylguanidine for treatment of resistant neuroblastoma: results of a UK study. Eur J Nucl Med 1991;18:308–16.
20. Buckley SE, Saran FH, Gaze MN, Chittenden S, Partridge M, Lancaster D, et al. Dosimetry for fractionated I131-mIBG therapies in patients with primary resistant high-risk neuroblastoma: preliminary results. Cancer Biother Radiopharm 2007;22 (1):105–12.
21. Chittenden S, Pratt B, Pomeroy K, Black P, Long C, Smith N, et al. Optimization of equipment and methodology for whole-body activity retention measurements in children undergoing targeted radionuclide therapy. Cancer Biother Radiopharm 2007;22(2):247–53.
22. MIRD Committee of Society of Nuclear Medicine. MIRD Dose Estimate Report No. 5. J Nucl Med 1975;16:587.
23. International Committee on Radiological Protection, ICRP Publication 53, Radiation dose to patients from radiopharmaceuticals, Annals of the ICRP, 18, 1–4 (1987).
24. International Committee on Radiological Protection, ICRP Publication 60, Recommendations of the International Commission on Radiological Protection, Annals of the ICRP, 21, 1–3 (1991).