Radiopharmaceutical diagnosis and therapy of sympatho-medullary disorders

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Key words: meta-iodobenzylguanidine (MIBG), sympathomedullary diseases, pheochromocytoma, neuroblastoma, neuroendocrine tumors

INTRODUCTION

This brief review seeks to summarize the current status of radiopharmaceutical diagnosis and therapy of sympathomedullary disorders at the time of the 35th Annual Meeting of the Japanese Society of Nuclear Medicine. Of necessity the references must be selective and will tend to emphasize previous reviews and the University of Michigan experience. It is now over 17 years since ¹²³I-metaiodobenzylguanidine (MIBG) was introduced for the scintigraphic location of pheochromocytomas and 15 years since its first use for the radiopharmaceutical therapy of malignant pheochromocytomas. In the USA ¹¹¹I-MIBG is now approved as a routine radiopharmaceutical for the scintigraphic location of pheochromocytomas, paragangiomas and neuroblastomas. Commercial provision of ¹¹¹I-MIBG and/or ¹³¹I-MIBG for these indications is now routine in most technologically advanced industrial countries.

Historical Background

The development of MIBG represented the successful culmination of many years of study involving the radiolabeled catecholamines, bretyllium analogs and finally the arylalkylguanidines.¹-³ The meta isomer of iodobenzylguanidine showed the least in vivo deiodination (although animal adrenal medullae were also scintigraphically depicted by the para isomer) and it was this that was used to visualize pheochromocytomas in man.³,⁴

Mechanisms of Uptake and Biodistribution

The uptake of MIBG by sympathomedullary tissues and tumors occurs by means of a specific, energy dependent, sodium dependent, high affinity, low capacity transporter of biogenic amines (the Type 1 mechanism).⁵,⁶ There is also a non-specific, passive, diffusional uptake into all tissues. From the cytoplasm further transport and storage occurs into the intracytoplasmic hormone storage granules.⁶ It thus follows that drugs that interfere with type 1 uptake (e.g. tricyclic antidepressants), granule storage (e.g. reserpine) or displacement of stored amines (e.g. cocaine) are contraindicated in MIBG scintigraphy.⁵,⁷ After intravenous injection MIBG is rapidly cleared from the blood with the majority being excreted unchanged in the urine (there is some specific uptake by platelets). Less than 2% is excreted in the feces.⁸

The normal biodistribution of MIBG (imaging with ¹³¹I-MIBG at 1, 2, 3 days and with ¹²³I-MIBG at 12–18 hours, 24 hours and 48 hours) includes specific uptake by the sympathethic innervation of the salivary glands, heart and spleen, and by the adrenal medulla; metabolic uptake by the liver; excretion into the gut, and excretion via the kidneys into the bladder.⁴,⁶ There is faint uptake in muscle and also into the brain but not in bone.⁵,⁸ Cardiac uptake is decreased in pheochromocytoma, probably due to hypercatecholaminemia competing for or down regulating the uptake 1 mechanism.⁵,⁸

Diagnostic Utility of ¹¹¹I-MIBG in Pheochromocytoma

Studies at the University of Michigan and subsequently confirmed and amplified by many other independent groups have shown ¹³¹I-MIBG to have excellent sensitivity (typically 80–90%) and specificity (typically 95–100%) for pheochromocytomas and non-secreting para-gangliomas of all types.¹,⁴,⁸-¹¹ This includes sporadic intra-adrenal pheochromocytomas, sporadic extra-adrenal pheochromocytomas (paragangliomas), malignant

Based on an invited lecture at the 34th Annual Scientific Meeting of the Japanese Society of Nuclear Medicine, Yokohama, October, 1995.

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metastatic and locally recurrent lesions. It is similarly effective for the pheochromocytomas associated with the neuroectodermal syndromes such as neurofibromatosis, von Hippel Lindau disease, multiple endocrine neoplasia types IIA and IIB and simple familial pheochromocytomas. 1,4,8-11

**Diagnostic Utility of 131I-MIBG in Neuroblastoma**
Rather similar results have been obtained in the study of neuroblastomas in which similar specificity and sensitivity have been recorded by many workers. 131I-MIBG scintigraphy permits the entire patient to be screened for tumor deposits in a single non-invasive, efficacious procedure which is particularly sensitive for spinal bone marrow invasion. 11-14

**Diagnostic Utility of 131I-MIBG in other APUDomas**
Many other neuroendocrine tumors of the amine precursor uptake and decarboxylation system (APUDomas) have been visualized by MIBG scintigraphy. These include; carcinoids, carcinoid body tumors, medullary thyroid cancers, islet cell tumors and Merkel cell tumors. 10,11,14-18
The experience is considerably less than for pheochromocytoma and neuroblastoma and so is the sensitivity (range 40–70%).

**Advantages of 123I-Labeled MIBG**
Despite the excellent results with 131I-MIBG in the scintigraphic depiction of pheochromocytomas and neuroblastomas and its approval for this in the USA by the FDA, the 131I-label is suboptimal for diagnostic imaging, having poor dosimetric and physical imaging characteristics. 1,19,23
The 8 day half-life which permits delayed imaging at times when background activity is low is perhaps its only imaging advantage (imaging is usually performed on days 1 to 3 but delayed imaging for a week or longer is occasionally performed and is also useful for radiation dosimetry in cases receiving large therapeutic doses of 131I-MIBG, vide infra). In contrast 123I has excellent physical properties for modern gamma camera imaging and delivers approximately 10% the radiation dose per unit activity. 12,11,19,20 Thus typical doses of 131I-MIBG are 0.5 to 1.0 mCi and 123I-MIBG 5.0 to 12.0 mCi. The quality of the images is far better and SPECT can also be performed. This results in somewhat greater sensitivity than with 131I-MIBG and far greater confidence.

The normal adrenal medulla are often visualized and the cardiac uptake is particularly well defined on 123I-MIBG scintigraphy. 6 SPECT permits the location of abnormal foci of MIBG uptake to be better defined in 3 dimensions and may also help counteract the effects of overlying activity (e.g. in gut). Thus where available 123I-MIBG must be considered the optimal radiopharmaceutical for most routine diagnostic purposes. 12,11,19,20

**Other Radiopharmaceuticals Based on MIBG**
MIBG labeled with 123I can be considered the parent compound for a whole series of radiopharmaceuticals for the study and treatment of the sympathoadrenal medullary system and its diseases. 1,2,11,19,23 This can be done by labeling MIBG with different forms of radiiodine for different purposes. Thus, 131I is used for routine imaging, dosimetric studies and radiotherapy. 1,2,20,24 123I is used for high quality diagnostic imaging and SPECT. 1,12,19,20 123I for biodistribution and autoradiographic studies in animals and as experimental radiotherapy of the bone marrow micrometastases of neuroblastoma, 21 123I for PET studies, including quantification for dosimetry. 20 An alternative is the use of other radiohalogens such as 125I and 127Br for PET or 211At for alpha particle radiotherapy (not yet performed in man). 20 A further variation is the use of related chemical compounds (e.g. 123I-4-amino-metaiodobenzylguanidine which can be labeled as a kit or 11C-hydroxyephedrine (HED) or 11C-epinephrine for PET studies which can be performed within 20 minutes of tracer injection). 20

**In Vivo Depiction of Autonomic Innervation**
MIBG and related radiopharmaceuticals provide a unique in vivo probe for the study of the presynaptic sympathetic innervation of the salivary glands and heart (uptake and vesicular storage pool). 1,2,6,8,25,26 MIBG uptake is strikingly reduced following surgical denervation of the salivary glands (Horner’s syndrome) and heart (e.g. epicardial phenol patch or heart transplantation). 6,8,25,27 The slow and partial reinnervation of the transplanted heart has also been depicted. The generalized denervation of autonomic neuropathy also reduces salivary gland and cardiac MIBG uptake (e.g. in diabetes, Shy-Draeger syndrome and idiopathic forms). 1,2,6,8

In a number of cardiac disorders there is also a reduction in uptake or more rapid clearance of MIBG which may be prognostic. 27,28 These include myocardial infarction (where the zone of denervation is larger than the infarct itself), congestive cardiac failure and various cardiomyopathies, including that due to cardiotoxic chemotherapy. Another area under active investigation is the search for abnormalities in cardiac innervation in various arrhythmias such as the familial long QT Syndrome.

**MIBG as a Therapeutic Radiopharmaceutical**
The excellent uptake, target to background ratio and prolonged retention of 111I-MIBG by many malignant and metastatic pheochromocytomas observed on diagnostic tracer studies has lead to its use, in large doses, for the delivery of therapeutic doses of radiation. 1,11,24,29,30 High specific activity 131I-MIBG (> 20 mCi/mg) is infused over 90 minutes and no acute pharmacological toxicity has been observed. In adults doses of 100 to 350 mCi have been administered. Dosimetric studies performed prior to therapy indicate whole body radiation doses of < 100–200 rads. The calculation of tumor radiation doses is more
difficult but in some cases it may considerably exceed 10,000 rad. In adults treated in this fashion radiation toxicity is mild to moderate with little myelosuppression: Most workers have treated patients with multiple (typically 3) doses in this fashion. The same principles have been applied to other MIBG avid tumors, particularly neuroblastomas and carcinoids. The MCi/kg and rad doses to the children with neuroblastomas have been greater than in adults and in some cases severe myelosuppression may occur. In the case of the hormonally hypersecretory tumors therapeutic response is evaluated by both objective tumor shrinkage and reduction in parameters of hormone secretion. The overall therapeutic responses for the experiences of multiple groups have been recently summarized by Hoefnagel as follows: Pheochromocytoma (116 evaluable patients, overall objective responses 55.9%, 3 complete responses); neuroblastoma (276 evaluable patients, overall objective responses 34.9%, 17 complete responses); MCT (22 evaluable patients, 31.8% overall objective responses, 1 complete response); carcinoid (52 evaluable patients, 15.4% objective responses, but 65.4% palliation and 2 complete responses).

While 123I-MIBG has been the principle therapeutic radiopharmaceutical there are theoretical reasons to believe that 125I may be more suitable to deliver radiation to micrometastases. Such lesions are typical of the bone marrow infiltration which occurs in neuroblastomas. Preliminary trials at the University of Michigan have shown the practicability of this approach (including solving the radiation protection problems due to the 60 day half-life of 125I) with doses as large as 600 mCi 125I-MIBG but the series treated was too small to accurately assess response rates.

Other Therapeutic Innovations
The vast majority of neuroblastoma patients selected for MIBG therapy have had very advanced disease, unresponsive to all standard therapies (and in many cases experimental therapies as well). Nevertheless, some therapeutic responses have been achieved (usually partial and palliative). More recently 123I-MIBG therapy has been instituted as initial therapy for neuroblastoma with encouraging results. In a few cases bulky lesions which are inoperable may be rendered operable by 123I-MIBG therapy. Other approaches include an experimental protocol under investigation at the University of Michigan which involves the use of 3 doses of 123I-MIBG (~300 mCi) at three month intervals followed by a series of chemotherapeutic treatments (vincristine, cyclophosphamide and DTIC) each of which has alone been shown to have significant therapeutic effect. The hypothesis to be tested is that the effects of the combined therapies will be more than additive. Other possibilities are the combination of 123I-MIBG (for large lesions) with 125I-MIBG (for micrometastases) or the delivery of alpha particle radiotherapy with 211At-meta-astitino-benzylguanidine.

Radiolabeled Somatostatin Analogs
An alternative approach to scintigraphy with MIBG (and its various analogs) for neuroendocrine tumors has been the development of radiolabeled somatostatin analogs which depict the binding of these tracers to cell surface receptors that are widely distributed on many neuroendocrine (and other) tissues and tumors. This in vivo depiction of somatostatin receptors closely follows that of autoradiographic in vitro depiction of the receptor, of which at least five different subtypes are now recognized. Various radiolabeled somatostatin analogs with different specificities for the various receptor subtypes are being investigated.

The newly developed 123I and 111In labeled somatostatin analogs (e.g. 111In-Octreoscan) would appear to be equal or slightly less in sensitivity than MIBG for pheochromocytomas and neuroblastomas and clearly superior for the other APUDomas. The somatostatin analogs, however, less specific for such lesions because they also bind to non-neuroendocrine lesions, including lymphomas, breast cancer, gliomas, meningiomas and inflammatory lymphocytes. Furthermore, radiotherapeutic somatostatin analogs are not yet available but are in development, (e.g. those with a 99Y label). Lesions that demonstrate in vivo binding of radiolabeled somatostatin analogs frequently respond to therapy with non-radioactive somatostatin analogs (e.g. Sandostatin/octetide).

ACKNOWLEDGMENTS
Due to space constraints many significant observations and contributions could not be individually referenced and I apologize to all workers in the field who may not have received the full recognition they warrant. I thank Ms. V. Rhodes for her help in preparation of the manuscript.

REFERENCES
6. Wafelmann AR, Hoefnagel CA, Maes RAA, Beijnen JM.


