Radiopharmaceutical diagnosis and therapy of sympatho-medullary disorders

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INTRODUCTION

THIS BRIEF REVIEWS 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 ^{131}I-meta-iodobenzylguanidine (MIBG) was introduced for the scientigraphic location of pheochromocytomas and 15 years since its first use for the radiopharmaceutical therapy of malignant pheochromocytomas. In the USA ^{131}I-MIBG is now approved as a routine radiopharmaceutical for the scintigraphic location of pheochromocytomas, paragangliomas and neuroblastomas. Commercial provision of ^{131}I-MIBG and/or ^{123}I-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, bretylium 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.[6]

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

Diagnostic Utility of ^{131}I-MIBG in Pheochromocytoma
Studies at the University of Michigan and subsequently confirmed and amplified by many other independent groups have shown ^{131}I-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

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 ^{131}I-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. ^{131}I-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 ^{131}I-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, carotid 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 ^{123}I-Labeled MIBG
Despite the excellent results with ^{131}I-MIBG in the scintigraphic depiction of pheochromocytomas and neuroblastomas and its approval for this in the USA by the FDA, the ^{131}I-label is suboptimal for diagnostic imaging, having poor dosimetric and physical imaging characteristics.[1,19,21] 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 ^{131}I-MIBG, vide infra). In contrast ^{123}I has excellent physical properties for modern gamma camera imaging and delivers approximately 10% the radiation dose per unit activity.[1,2,11,19,20] Thus typical doses of ^{131}I-MIBG are 0.5 to 1.0 mCi and ^{123}I-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 ^{131}I-MIBG and far greater confidence.

The normal adrenal medulae are often visualized and the cardiac uptake is particularly well defined on ^{123}I-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 ^{123}I-MIBG must be considered the optimal radiopharmaceutical for most routine diagnostic purposes.[1,2,11,19,20]

Other Radiopharmaceuticals Based on MIBG
MIBG labeled with ^{131}I can be considered the parent compound for a whole series of radiopharmaceuticals for the study and treatment of the sympathoadrenalmedullary system and its diseases.[1,2,11,19–23] This can be done by labeling MIBG with different forms of radioiodine for different purposes. Thus, ^{131}I is used for routine imaging, dosimetric studies and radiotherapy,[1,2,20,24] [123]I is used for high quality diagnostic imaging and SPECT.[1,2,19,20] [125]I for biodistribution and autoradiographic studies in animals and as experimental radiotherapy of the bone marrow micrometastases of neuroblastoma,[22] [124]I for PET studies, including quantification for dosimetry.[20] An alternative is the use of other radiohalogens such as ^{18}F and [67]Br for PET or [211]At for alpha particle radiotherapy (not yet performed in man).[20] A further variation is the use of related chemical compounds (e.g. ^{123}I-4-amino-metaiodobenzylguanidine which can be labeled as a kit or ^{11}C-hydroxyephedrine (HED) or ^{11}C-epinephrine for PET studies which can be performed within 20 minutes of tracer injection).[20,21,23]

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).[6,8,26,27] The slow and partial renervation 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-Drager 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 ^{131}I-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.[2,11,24,29,30] High specific activity ^{131}I-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.[11,17,24,29,30] 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[10,11,29,30] 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 ^{131}I-MIBG has been the principle therapeutic radiopharmaceutical there are theoretical reasons to believe that ^{125}I may be more suitable to deliver radiation to micrometastases.[20,22] 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 ^{125}I) with doses as large as 600 mCi ^{125}I-MIBG but the series treated was too small to accurately assess response rates.[20,22]

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).[2,11,12,30] Nevertheless, some therapeutic responses have been achieved (usually partial and palliative). More recently ^{131}I-MIBG therapy has been instituted as initial therapy for neuroblastoma with encouraging results.[12,30,31] In a few cases bulky lesions which are inoperable may be rendered operable by ^{131}I-MIBG therapy. Other approaches include an experimental protocol under investigation at the University of Michigan which involves the use of 3 doses of ^{131}I-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 ^{131}I-MIBG (for large lesions) with ^{125}I-MIBG (for micrometastases) or the delivery of alpha particle radio-

therapy with [211]At-meta-astitino-benzylguanidine.[20,22]

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.[11,32,33] 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 ^{123}I and ^{111}In labeled somatostatin analogs (e.g. ^{111}In-Octreoscan) would appear to be equal or slightly less in sensitivity than MIBG for pheochromocytomas and neuroblastomas and clearly superior for the other APUDomas.[11,32,33] The somatostatin analogs, are however, less specific for such lesions because they also bind to non-neuroendocrine lesions, including lymphomas, breast cancer, gliomas, meningiomas and inflammatory lymphocytes.[11,32-34] Furthermore, radiotherapeutic somatostatin analogs are not yet available but are in development, (e.g. those with a ^{90}Y label). Lesions that demonstrate *in vivo* binding of radiolabeled somatostatin analogs frequently respond to therapy with non-radioactive somatostatin analogs (e.g. Sandostatin/octreotide).[11,22,33]

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REFERENCES

1. Shapiro B, Sisson JC. Sympatho-adrenal imaging with radio-iodinated meta-iodobenzylguanidine. *In* Atlas of Nuclear Medicine, Van Nostrand D, Baus S (eds.), Philadelphia, Lippincott, pp. 72–114, 1988.
2. Shapiro B. Imaging of catecholamine-secreting tumors: uses of MIBG in diagnosis and treatment. *Bailliere's Clinical Endocrinology and Metabolism* 7 (2): 491–507, 1993.
3. Wieland DM, Swanson DP, Brown LE, Beierwaltes WH. Imaging the adrenal medulla with an ^{131}I-labeled anti-adrenergic agent. *J Nucl Med* 20: 155–158, 1979.
4. Sisson JC, Frager MS, Valk TW, Gross MD, Swanson DP, Wieland DM, et al. Scintigraphic localization of pheochromocytoma. *N Engl J Med* 305: 12–17, 1981.
5. Tobes MC, Jaques S, Wieland DM, Sisson JC. Effect of uptake-one inhibitors on the uptake of norepinephrine and metaiodobenzylguanidine. *J Nucl Med* 26: 897–907, 1985.
6. Wafelman AR, Hoefnagel CA, Maes RAA, Beijnen JM.

Radioiodinated metaiodobenzylguanidine: a review of its biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry. *Eur J Nucl Med* 21: 545–559, 1994.

7. Khafagi FA, Shapiro B, Fig LM, Mallette S, Sisson JC. Labetalol reduces iodine-131-MIBG uptake by pheochromocytoma and normal tissues. *J Nucl Med* 30: 481–489, 1989.

8. Nakajo M, Shapiro B, Copp J, Kalff V, Gross MD, Sisson JC, et al. The normal and abnormal distribution of the adrenomedullary imaging agent in I-131-iodobenzylguanidine (I-131-MIBG) in man: Evaluation by scintigraphy. *J Nucl Med* 24: 762–782, 1983.

9. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. *Endocrine Reviews* 15: 356–368, 1994.

10. Hoefnagel CA, Voûte PA, de Kraker J, Marcuse HR. Radionuclide diagnosis and therapy of neural crest tumours using iodine-131 metaiodobenzylguanidine. *J Nucl Med* 38: 308–314, 1987.

11. Hoefnagel CA. Metaiodobenzylguanidine and somatostatin in oncology: role in the management of neuralcrest tumors. *Eur J Nucl Med* 21: 561–581, 1994.

12. Gelfand MT. Metaiodobenzylguanidine in children. *Semin Nucl Med* 23: 231–242, 1993.

13. Kimmig B, Brandeis WE, Eisenhut M, Bubeck B, Hermann HJ, zum Winkel K. Scintigraphy of a neuroblastoma with I-131-metaiodobenzylguanidine. *J Nucl Med* 25: 773–775, 1984.

14. Troncone L, Rufini V, Montemaggi P, Danza FM, Lasorella A, Mastrangelo R. The diagnosis and therapeutic utility of radioiodinated metaiodobenzylguanidine (MIBG). 5 year's experience. *Eur J Nucl Med* 16: 325–335, 1990.

15. Clarke SEM, Lazarus CR, Wraight P, Sampson C, Maisey MN. Pentavalent [^{99m}Tc]DMSA, [^{131}I]MIBG, and [^{99m}Tc]MDP—An evaluation of three techniques in patients with medullary carcinoma of the thyroid. *J Nucl Med* 29: 33–38, 1988.

16. Fischer M, Kamanabroo D, Sonderkamp H, Proske T. Scintigraphic imaging of carcinoid tumours with ^{131}I-meta-iodobenzylguanidine. *Lancet* 11: 165, 1984.

17. McEwan AJ, Catz Z, Fields AL, Lewington V, Harbora D, Fine D, Ackery DM. I-131 meta iodobenzylguanidine (mIBG) in the diagnosis and treatment of carcinoid syndrome. *J Nucl Med* 28: 658, 1987.

18. Von Moll L, McEwan AJ, Shapiro B, Sisson JC, Gross MD, Lloyd R, et al. Iodine-131 MIBG scintigraphy of neuroendocrine tumours others than pheochromocytoma and neuroblastoma. *J Nucl Med* 28: 979–988, 1987.

19. Mozley PD, Kim DK, Mohsin J, Jatlow A, Gosfield E, Alavi A. The efficacy of Iodine-123-MIBG as a screening test for pheochromocytoma. *J Nucl Med* 35: 1138–1144, 1994.

20. Shapiro B, Gross MD. Radiochemistry, biochemistry and kinetics of ^{131}I-MIBG and ^{123}I-MIBG: Clinical implications of the use of ^{123}I-MIBG. *Med Pediatr Oncol* 15: 170–177, 1987.

21. Shulkin B, Wieland DM, Schwaiger M, Thompson NW, Haka M, Rosenspire KC, et al. PET scanning with hydroxyephedrine: A new approach to the localization of pheochromocytoma. *J Nucl Med* 33: 1125–1131, 1992.

22. Sisson JC, Hutchinson RJ, Shapiro B, Zasadny KR, Normolle D, Wieland DM, et al. Iodine 123-I-MIBG to treat neuroblastoma: Preliminary report. *J Nucl Med* 31: 1479–1485, 1990.

23. Shulkin B, Shapiro B, Tobes MC, Shen SW, Wieland DM, Meyers L, et al. 125-I-4-amino-3-iodobenzylguanidine (123-I-AIBG), a new sympathoadrenal imaging agent: Comparison with 123-I-metaiodobenzylguanidine (123-I-MIBG). *J Nucl Med* 27: 1138–1142, 1986.

24. Sisson JC, Shapiro B, Beierwaltes WH, Glowniak JV, Nakajo M, Mangner TJ, et al. Radiopharmaceutical treatment of malignant pheochromocytoma. *J Nucl Med* 24: 197–206, 1984.

25. Nakajo M, Shapiro B, Glowniak JV, Sisson JC, Beierwaltes WH. Inverse relationship between cardiac accumulation of Meta-[^{131}I]-Iodobenzylguanidine (I-131-MIBG) and circulating catecholamines: Observations in patients with suspected pheochromocytoma. *J Nucl Med* 24: 1127–1134, 1983.

26. Nakajo M, Shapiro B, Sisson JC, Swanson DP, Beierwaltes WH. Salivary gland accumulation of meta-[^{131}I]iodobenzyl-guanidine. *J Nucl Med* 25: 2–6, 1984.

27. Sisson JC, Lynch JJ, Johnson J, Jaques S, Wu D, Bolgos G, et al. Scintigraphic detection of regional disruption of adrenergic neurons in the heart. *Am Heart J* 116: 67–76, 1988.

28. Merlet P, Valette H, Dubois-Randé JL, Moyse D, Duboc D, Dove P, et al. Prognostic value of cardiac metaiodobenzyl-guanidine imaging in patients with heart failure. *J Nucl Med* 33: 471–477, 1992.

29. Hoefnagel CA, Taal BG, Valdés Olmos RAZ. Role of I-131 MIBG therapy in carcinoids. *J Nucl Biol Med* 35: 346–348, 1991.

30. Troncone L, Galli G. Proceedings of the international workshop on the role of [^{131}I]metaiodobenzylguanidine in the treatment of neural crest tumours. *J Nucl Biol Med* 35: 177–362, 1991.

31. Hoefnagel CA, de Kraker J, Voûte PA, Valdés Olmos RA. Preoperative I-131-MIBG therapy of neuroblastoma at diagnosis ("MIBG *de novo*"). *J Nucl Biol Med* 35: 248–251, 1991.

32. Krenning EP, Bakker WH, Kooij PPM, Breeman WAP, Oei HY, de Jong M, et al. Somatostatin receptor scintigraphy with indium-111-DTPA-D-Phe-1 octreotide in man: metabolism, dosimetry and comparison with iodine-123-Tyr-3-octreotide. *J Nucl Med* 33: 652–658, 1992.

33. Krenning EP, Kwekkeboom DJ, Bakker WH, Breeman WAP, Kooij PPM, Oei HY, et al. Somatostatin receptor scintigraphy with [^{111}In-DTPA-D-Phe^{1}]- and [^{123}I-Tyr^{3}]-octreotide: the Rotterdam experience with more than 1000 patients. *Eur J Nucl Med* 10: 7167-31, 1993.

34. Schneidhauer K, Göhring U-J, Scharl AM, Voth E, Theissen P, Schomäcker K, et al. Somatostatin-receptor-imaging in breast tumours. *Eur J Nucl Med* 20: 973, 1993.