Role of Iodine-131 MIBG Scanning in the Management of Paediatric Patients with Neuroblastoma

G.M. Shah Syed^a H. Naseer^b G.N. Usmani^b M.A. Cheema^b

^aDepartment of Nuclear Medicine, Faculty of Medicine Kuwait University, Kuwait, and

^bShaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore, Pakistan

Key Words

Iodine-131 MIBG imaging · Correlative imaging · Neuroblastoma · Bone marrow involvement · Bone scanning

Abstract

Objectives: To evaluate the role of iodine-131 metiodo-benzylguanidine (iodine-131 MIBG) scanning in the management of paediatric patients with neuroblastoma. **Subjects and Methods:** Forty-three iodine-131 MIBG scans were performed on 26 children, 18 male and 8 female, ranging in age from 8 months to 11 years. Bone scan, computed tomography (CT) images and findings of bone marrow biopsy were compared with the iodine-131 MIBG scan findings. **Results:** Of the 26 patients, 18 (69%) showed abnormal iodine-131 MIBG avidity and were proven to have a neural crest tumour on histology. The remaining 8 (31%) patients had normal iodine-131 MIBG scans, and histology showed a malignancy other than a neural crest tumour. Iodine-131 MIBG scans showed the primary site in 16 of 17 patients while CT showed 14 primary sites. In follow-up studies, the results were as follows: iodine-131 MIBG showed no evidence of disease in 4 compared with 3 on CT, persistent disease in 2 on iodine-131 MIBG and 4 on CT; recurrence in 1 on iodine-131 MIBG and 0 on CT; MIBG scans detected double the number of bony lesions compared with bone scans. The

findings on iodine-131 MIBG scans and bone marrow biopsy were in agreement in 16/18 cases. Patients in whom iodine-131 MIBG scans showed disease resolution had better clinical outcomes. **Conclusion:** The findings indicate that iodine-131 MIBG scanning is useful for the diagnosis, staging, evaluation of response to therapy and detection of recurrences in patients with neuroblastoma. It exhibited a clear advantage over CT in detecting the primary site and soft tissue metastases and was also superior to bone scanning in detecting skeletal metastases. It also reliably demonstrated bone marrow involvement.

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Introduction

Neuroblastoma is one of the most common solid tumours in children. Approximately 80% of patients with neuroblastoma are under the age of 5 years [1]. Arising from neural crest cells, neuroblastoma is found in a variety of locations such as the adrenal medulla, the sympathetic chain, the posterior mediastinum, pelvis, cervical region and rarely in the posterior cranial fossa. The diagnosis and staging of neuroblastoma require measuring urinary catecholamine levels, a plain radiography, an intravenous pyelogram, an ultrasonogram, a CT or an MRI scan of the region and a bone scan. Biopsy provides the

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G.M. Shah Syed, Ass. Prof.
Department of Nuclear Medicine, Faculty of Medicine
Kuwait University, PO Box 24923
Safat 13110 (Kuwait)
Tel. +965 4815578, Fax +965 5338936, E-Mail gmsahsyed@hotmail.com

final histological diagnosis. Light microscopy supplemented by electron microscopy and immuno-histochemical techniques helps to differentiate neuroblastoma from other round blue-cell tumours. The bone marrow biopsy helps to detect bone marrow involvement. Many studies have shown the usefulness of radiolabelled iodine-131 MIBG imaging in patients with neuroblastoma in establishing diagnosis, tumour staging, prognosis and assessing the response to treatment [2–6]. Sensitivity and specificity of the test are above 85 and 94%, respectively [7, 8]. This study was done to evaluate the role of iodine-131 MIBG in the diagnosis, staging and response to treatment in pediatric populations with neural crest tumours and compare the findings to those of bone scan and bone marrow biopsy.

Subjects and Methods

Twenty-six (18 male and 8 female) consecutive patients, during a four year period (1996–1999), under the age of 17 years with a histopathologically confirmed diagnosis or clinical suspicion of neuroblastoma were included in the study. Median age and standard deviation at the time of diagnosis was 5 ± 3 years and ranged from 8 months to 17 years. For each patient, the history was recorded and a physical examination and clinical diagnosis were performed. CT, urinary catecholamine levels and bone marrow biopsy were performed in all 26 patients while bone scans were done only in 12 patients with positive iodine-131 MIBG studies.

Prior to administration of iodine-131 MIBG, it was ensured that no patient was taking any medication that could interfere with the uptake of iodine-131 MIBG. Ten drops of Lugol's solution were given to each patient 1 day before the injection and patients were advised to keep on taking it for 7 days thereafter in order to block the uptake of iodine-131, a metabolic product of iodine-131 MIBG, by the thyroid gland. Each patient was injected slowly with iodine-131 MIBG intravenously (M/S, Amersham, UK). The administered dose was 0.5–1 MBq (0.01–0.03 mCi)/kg body weight, not exceeding 18.5 MBq (0.5 mCi). In each case, scans were acquired on a digital camera (Diacam from M/S Siemens) at 24, 48 and 72 h after dose administration. A 15% window was set on the 364 keV photo peak. Each image was acquired for 15 min or 110 K counts, whichever came first, using a high-energy general-purpose collimator. The matrix size was set at $64 \times 64 \times 8$. Planar anterior and posterior views of the neck, chest, abdomen and pelvis were taken. Imaging of the limbs was carried out at either 48 or 72 h. A zoom factor of 1.23 was applied on small children. Younger patients were sedated with a single oral dose of promethazine 0.5 mg/kg. The acquired images were then copied onto a radiographic film and images were interpreted visually with consensus between two nuclear physicians who were aware of the clinical diagnosis but blinded to the findings of other imaging and laboratory investigations. Patterns of iodine-131 MIBG not consistent with the normal distribution were considered as evidence of iodine-131 MIBG-avid disease. Focal uptake of iodine-131 MIBG in bones was considered a metastatic bony lesion. Diffuse uptake at the growing ends of the long bones or throughout

Table 1. Histological diagnosis and abnormal ^{131}I MIBG avidity

Histological diagnosis	MIBG scan	
	positive	negative
1 Neuroblastoma or related tumour (n = 18)	18	0
2 Ewing sarcoma (n = 2)	0	2
3 Primitive neuroectodermal tumour (n = 2)	0	2
4 Retinoblastoma (n = 2)	0	2
5 Rhabdomyosarcoma (n = 1)	0	1
6 Ganglioneuroma (n = 1)	0	1

the skeleton was considered as positive for bone marrow involvement.

Technetium-99m methylene diphosphonate (Tc-99m MDP, M/S) was used for bone scanning. A dose of 5,555 MBq (15 mCi)/kg body weight of Tc-99m MDP was injected intravenously. Scanning was performed 3 h after dose administration. For acquisition, matrix size was set at $128 \times 128 \times 128$, with a 15% energy window centred at 140 keV. A zoom factor of 1.23 was used for small children. Overlapping static images of the skull, pelvis, chest and spine were acquired in anterior and posterior projections using a low-energy general purpose collimator. The posterior spine image was acquired for 750 K counts while all other views were acquired for this same time period. Anterior views of the lower limbs were also acquired for 5 min. The acquired images were then copied onto radiographic films.

Results

Of the 26 patients, 18 (69%) had positive iodine-131 MIBG scans and were proven histologically to have neuroblastoma. One of these patients had the primary site surgically removed prior to iodine-131 MIBG scanning, but was positive due to metastasis to the soft tissues. The remaining 8 patients had normal iodine-131 MIBG scans but histologically were shown to have non-neuroblastoma tumours (table 1).

Table 2 shows the comparison between iodine-131 MIBG and the CT scans. Iodine-131 MIBG scans showed the primary site in 17 of the 18 patients with histologically proven neural crest tumour while CT detected primary lesions in 14 patients.

In 7 patients, 12 follow-up iodine-131 MIBG scans were compared with CT scans. Iodine-131 MIBG scans showed disease resolution in 4 patients (6 studies), persistent disease in 2 patients (5 studies) and recurrence was noted in 1 patient. CT scan showed disease resolution in 3 patients (4 studies) and persistent disease in 4 patients (8 studies).

Fig. 1. a Iodine-131 MIBG-avid lesions in lower abdomen and pelvis (arrows) which are not seen on corresponding CT slices (**b**).

Table 2. Comparison of MIBG and CT scanning in patients with neuroblastoma

	MIBG		CT	
	positive	negative	positive	negative
<i>Baseline study</i>				
Primary disease only	7	0	6	1
Primary lesion and metastatic disease	9	0	8	1
Metastatic disease only	1	0	0	1
<i>Follow-up studies</i>				
Disease-free	0	4	1	3
Partial/persistent disease	2	0	1	1
Recurrent disease	1	0	0	1

In the head, neck and chest regions, findings on 14 iodine-131 MIBG studies and corresponding CT scans were in complete agreement. In the abdominal region, however, 18 iodine-131 MIBG studies showed abnormal avidity while the CT examination detected lesions in only 16. Four pelvic CT scans were available for comparison

with iodine-131 MIBG pelvis views. In 1 case the results were similar; however, in 3 patients, the CT scan missed some of the lesions. Figure 1a shows an iodine-131 MIBG scan acquired 48 h after injection. Abnormal tracer accumulation in abdomen and pelvis is noted. Corresponding CT slices (fig. 1b) failed to show any abnormality.

Fig. 2. Iodine-131-MIBG scan acquired 48 h post injection in a patient with neuroblastoma. Diffuse symmetrical uptake in skeleton is highly suggestive of bone marrow involvement.

Twelve bone scans were available for comparison with iodine-131 MIBG studies. Seven bone scans were positive for metastases and a total of 13 lesions were seen. Iodine-131 MIBG scans were positive for metastases in 6/7 of these cases and a total of 24 lesions were seen. Hence 12 additional sites of bony metastasis were seen on iodine-131 MIBG scans. In 1 case, the iodine-131 MIBG scan did not show a lesion noted on the bone scan.

Eighteen iodine-131 MIBG scans were compared with the results of bone marrow biopsy performed at the same time. The results of 16 iodine-131 MIBG scans and corresponding bone marrow biopsies were in complete agreement (5 positive and 11 negative). In 2 patients the bone marrow biopsies were positive but the iodine-131 MIBG scan did not show bone marrow involvement. Figure 2 shows a positive iodine-131 MIBG scan acquired 48 h after injection with symmetrical skeletal uptake suggestive of extensive bone marrow involvement. A 3-year follow-up was available in 8/18 patients. Three patients showed complete resolution of the disease on follow-up iodine-131 MIBG scans and were still clinically stable. One scan showed resolving disease and the patient was alive (follow-up period of 21 months). In another patient where the iodine-131 MIBG scan showed resolution of lesions, death occurred during treatment due to complications from chemotherapy. The remaining 3 patients had persistent iodine-131 MIBG avid lesions and died from the disease within 12 months of follow-up.

Discussion

Accurate tumour staging is necessary for therapeutic decision making and assessment of prognosis in patients with neuroblastoma. Iodine-131/123 MIBG, the radiolabelled analogue of norepinephrine, is taken up by the

functioning neuroblastoma. Fibrotic or necrotic tumours do not accumulate this radiopharmaceutical. Post-treatment uptake of the radioiodine-labelled MIBG helps in monitoring the response of the lesions to therapy. Thus iodine-131/123 MIBG scintigraphy is a simple non-invasive test that helps in diagnosing, staging and monitoring response to therapy with high sensitivity and specificity [9, 10]. Although iodine-123 MIBG produces a better image quality and localization of lesion than iodine-131 MIBG [11, 12], the latter was used in this study due to difficulty in procuring iodine-123 MIBG because iodine-123 has a short half-life of 13 h.

In our study, all patients who had abnormal accumulation of iodine-131 MIBG were proven to have neuroblastoma or a related tumour while those who had a negative iodine-131 MIBG scan had a tumour other than neuroblastoma. Hence, in this study population there was no false-positive or false-negative case, thereby giving a sensitivity and specificity of 100%, each consistent with previously published reports [13–16].

In comparing iodine-131 MIBG findings with those of CT, iodine-131 MIBG scanning had a clear advantage over CT as it detected not only the primary site in all patients (CT missed two), but also more lesions than CT. Iodine-131 MIBG also provided accurate information on the functional status of the disease in 6 cases where CT failed to detect or underestimated the disease. Similar findings regarding the lower sensitivity and specificity of CT have been reported by Lastoria et al. [17]. In addition, CT may detect residual masses while the iodine-131 MIBG scan is normal because only iodine-131 MIBG scanning can confirm the viability of a tumour [17]. In this study there were 2 such cases plus a third in which iodine-131 MIBG detected a recurrence on follow-up scans, while the CT scan failed to do so. Overall, iodine-131 MIBG was more helpful than CT in localising the pri-

mary site, accurately staging the disease by detecting metastatic sites, in differentiating between active disease and fibrosis and in detecting recurrences, as has been previously reported [18]

In comparison to bone imaging, the extent of bony involvement was higher on iodine-131 MIBG scan than on bone scans; in fact iodine-131 MIBG detected twice the number of lesions compared with bone scans. Only one patient had a positive bone scan when the iodine-131 MIBG scan findings were negative. In this patient the iodine-131 MIBG scan failed to detect a skull lesion. This could be a false-negative finding; but it is possible that the lesion in the skull on the bone scan was a benign process. Localised radiographs could not be done to establish the nature of the lesion. However, bone scanning offers better site localisation than iodine-131 MIBG scanning. Similar findings have been reported previously [8].

Previous studies have described a pattern on iodine-131 MIBG scans that is highly suggestive of bone marrow involvement. This pattern has been shown as symmetrical

uptake in vertebrae, pelvis and other bones [19]. Whenever iodine-131 MIBG is positive, the likelihood of bone marrow involvement is high, as shown in this study where all 5 positive iodine-131 MIBG were also positive on bone marrow biopsy. However, there remains a possibility of missing bone marrow involvement based on iodine-131 MIBG scanning as in this study, where 2 of 7 patients were negative.

Conclusion

The findings indicate that iodine-131 MIBG scanning is useful for the diagnosis, staging, assessment of response to therapy and in detecting recurrences in patients with neuroblastoma. It has a clear advantage over CT in detecting the primary site and soft tissue metastases. It is also superior to bone scanning in detecting skeletal metastases. It also reliably demonstrates bone marrow involvement.

References

- Philip A, Pizzo MD, David G: Principles and Practice of Pediatric Oncology, ed 2. Philadelphia, Lippincott, 1989, pp 739–741.
- Suc A, Lumbroso J, Rubie H, Hattchouel JM, Boneu A, Rodary C, Robert A, Hartmann O: Metastatic neuroblastoma in children older than one year: Prognostic significance of the initial metaiodobenzylguanidine scan and proposal for a scoring system. *Cancer* 1996;77: 805–811.
- Perel Y, Conway J, Kletzel M, Goldman J, Weiss S, Feyler A, Cohn SL: Clinical impact and prognostic value of metaiodobenzylguanidine imaging in children with metastatic neuroblastoma. *J Pediatr Hematol Oncol* 1999;21: 13–18.
- Hugosson C, Nyman R, Jorulf H, McDonald P, Rifai A, Kofide A, Jacobsson B: Imaging of abdominal neuroblastoma in children. *Acta Radiol* 1999;40:534–542.
- Turba E, Fagioli G, Mancini AF, Rosito P, Galli A, Alvisi P: Evaluation of stage 4 neuroblastoma patients by means of MIBG and Tc-99m MDP scintigraphy. *J Nucl Biol Med* 1993;37: 107–114.
- Sisson JC, Shulkin BL: Nuclear medicine imaging of pheochromocytoma and neuroblastoma. *Q J Nucl Med* 1999;43:217–223.
- Fischer M, Galanski M, Winterberg B, Vatter H: Localization procedures in pheochromocytoma and neuroblastoma. *Cardiology* 1985;72: 143–146.
- Shulkin BL, Shapiro B: Current concepts on the diagnostic use of MIBG in children. *J Nucl Med* 1998;39:679–688.
- Greggiani M, Varotto L, Zucchetta P, Macri C: Nuclear medicine methods for the diagnosis of adrenal tumours. *Minerva Endocrinol* 1995; 20:27–38.
- Heinz-Peer G, Honigschnabl S, Niederle B, Lechner G: Characterization of adrenal gland space-occupying lesions. Can diagnostic imaging replace biopsy? *Radiologe* 1999;39:578–583.
- Swart J, de Kraker, van der Lely N: Metaiodobenzylguanidine total body scintigraphy required for revealing occult neuroblastoma in oposoclonus-myoclonus syndrome. *Eur J Pediatr* 2002;161:255–258.
- Gelfand M, Elgazzar A, Kriss V, Masters P, Golsch G: Iodine-123-MIBG SPECT versus planar imaging in children with neural crest tumours. *J Nucl Med* 1994;35:1753–1757.
- Muller-Gartner HW, Erttmann R, Helmke K: Die Szintigraphie mit Radiojod-[Meta-Jod-Benzylguanidin] in der Diagnostik des Neuroblastoms. *Nuklearmedizin* 1985;24:222–226.
- Odano I, Masayuki T, Saka K: Significance of I-131 meta-iodobenzylguanidine scintigraphy in diagnosing neuroblastoma. *Kaku Igaku* 1986;11:1685–1688.
- Hadley GP, Rabe E: Scanning with iodine 131-MIBG in children with solid tumours: An initial appraisal. *J Nucl Med* 1986;27:620–626.
- Feine U, Muller-Schauenburg W, Treuner J, Klingebiel T: Metaiodo-benzyl guanidine (MIBG) labelled with I-123/I-131 in Neuroblastoma diagnosis and follow-up treatment with a review of the diagnostic results of the International Workshop of Pediatric Oncology Held in Rome, September 1986. *Med Pediatr Oncol* 1987;15:181–187.
- Lastoria S, Maurea S, Caraco C, Vergara E, Maurelli L, Indolfi P, Casale F, di Tullio MT, Salvatore M: Iodine-131 metaiodobenzylguanidine scintigraphy for localization of lesions in children with neuroblastoma: Comparison with computed tomography and ultrasonography. *Eur J Nucl Med* 1993;20:1161–1167.
- Murashima S, Takeda K, Okuda Y, Nakagawa T, Sakurai M: Assessment of the biological activity of residual or recurrent neuroblastoma tumours with ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy. *Kaku Igaku* 1990;27: 1393–1400.
- Claudian F, Stimamiglio P, Bertolazzi L: Radioiodinated meta-iodo benzyl guanidine in the diagnosis of childhood neuroblastoma. *Q J Nucl Med* 1995;39:21–24.