Quantitative Study of Radioiodinated Metaiodobenzylguanidine Uptake in Children with Neuroblastoma: Correlation with Tumor Histopathology

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Six children with neuroblastoma and one with ganglioneuroma received [^{125}I] metaiodobenzylguanidine (MIBG) before major surgery. Uptake of [^{125}I]MIBG in the excised tissues was measured by scintillation counting, and the material was submitted for histopathology. The ranges of uptake of [^{125}I]MIBG, expressed as percent of the injected dose per gram of tissue, were as follows: for neuroblastoma 0.0013-0.071, for ganglioneuroma 0.0017-0.0028, and for non-neoplastic control tissues 0.0002-0.011. The quantitative uptake of [^{125}I]MIBG by neuroblastoma varied between different patients and between different parts of individual tumors. The more undifferentiated tumors took up more [^{125}I]MIBG and may be more likely to respond to targeted radiotherapy with MIBG.

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Neuroblastoma is the third most common childhood tumor, accounting for ~8% of malignancies in children under the age of 15 years (*1*). Although 60–70% of children with stage III and IV disease achieve complete clinical remission with current therapy, the disease will eventually relapse in the majority; children who are more than 1 yr old and have widespread disease at diagnosis attain a 4-yr disease-free survival of only 30% (*2*). New ways of approaching the therapy of neuroblastoma clearly need to be devised in an attempt to improve the cure rates.

Metaiodobenzylguanidine (MIBG) is a pharmacologic analog of the false neurotransmitter guanethidine and was first described as an imaging agent for the adrenal medulla (*3*). Various investigators have subsequently demonstrated the high affinity with which MIBG localizes in adrenergic tissues and their associated tumors, notably pheochromocytoma (*4*) and neuroblastoma (*5*). The uptake mechanism of MIBG for these tissues is thought to be similar to that of noradrenaline, with the neuronal uptake 1 system predominating at blood levels associated with clinical usage (*6*). In adrenergic tissues, MIBG appears to localize within chromaffin storage granules so that, at least for normal tissues, uptake and storage of MIBG is similar to noradrenaline (*7*). For imaging purposes MIBG can be labeled with iodine-123 (^{123}I) or iodine-131 (^{131}I); it can also be labeled with iodine-125 (^{125}I) ($T_{½}$ = 60 days) for in vitro studies.

MIBG has been used as a means of targeted radiotherapy for both neuroblastoma and pheochromocytoma. Encouraging results have been achieved in some children with neuroblastoma, but in others it has been disappointing. At the IVth International Workshop in Pediatric Oncology (*8*) devoted to, "MIBG in therapy, diagnosis and monitoring of neuroblastoma", it was shown that MIBG (used as a therapeutic agent) induced some kind of remission in ~ 35% of patients with relapsed, heavily pre-treated disease.

The quantitative uptake of MIBG by the tumor can (in theory) be determined from MIBG scans. Our gamma camera estimates of MIBG uptake by neuroblastomas show only a partial correlation with the

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actual uptake derived from in vitro measurements (*9*). We were therefore concerned that calculations of tumor uptake based on MIBG scintigraphy would not be sufficiently accurate to estimate dosimetry and response to MIBG therapy. The following study was therefore planned. Iodine-125 MIBG would be administered intravenously to children, prior to undergoing routine surgical excision of their tumors. The study had two main aims: to measure the range of [^{125}I]MIBG uptake in a series of excised neuroblastomas and related tumors in children, and to correlate quantitative uptake of MIBG with tissue morphology.

MATERIALS AND METHODS

Seven children took part in this study—three females and four males aged between 10 mo and 12 yr 9 mo with a median of 5.1 yr. A pre-operative diagnosis of neuroblastoma had already been made in six of the children from a biopsy and raised urinary catecholamines, and in the seventh child the clinical history, marginally raised urinary catecholamines and a computed tomography (CT) scan suggested a diagnosis of ganglioneuroma.

All seven children were scheduled to undergo routine resection of their tumors at various stages in the course of the disease. Prior to surgery the project was explained to the families and informed consent obtained. The protocol was approved by the hospital ethical committee. A drug sheet was provided, listing the prescribed drugs and over-the-counter preparations that were known or thought to interfere with MIBG uptake, and therefore to be avoided during the 6 wk before surgery.

The [^{125}I]MIBG used in this study was prepared by solid-phase iodine for iodine exchange using cold MIBG (CIS kit, IK4, Gif-sur-Yvette, France) and reacting it with ^{125}I-NaI (IMS.30, Amersham International, Amersham, UK) in the presence of ammonium sulfate. Terminal sterilization was accomplished using 0.22-μm filtration (GS, Millipore Corp., Bedford, MA). Radiochemical purity was determined by silica gel thin layer chromatography using two solvent systems; ethanol:ethyl acetate (1:1) (MIBG Rf = 0.0, I^- Rf = 0.6) and n-propanol : 10% ammonium hydroxide (3:1) (MIBG Rf = 0.15, I– Rf = 0.75). Initially thin-layer chromatographs were compared with chromatographs from reverse phase high performance liquid chromatography (Bio-Sil (Bio-Rad, Richmond, CA) ODS-5S, 150 mm × 4 mm) using THF/0.1*M* sodium phosphate (12:88) (retention time ≃ 8 min @ 2ml/min) in order to verify radiochemical purity. The solid-phase exchange consistently yielded > 95% [^{125}I]MIBG.

In order to block uptake of free iodine by the thyroid, Lugol's iodine (0.2 ml by mouth, three times a day) was started 48 hr before the [^{125}I]MIBG was given, and continued for 1 wk. Twenty-four to forty-eight hours before surgery 18 MBq [^{125}I]MIBG were administered intravenously over 90 sec. The exact amount of [^{125}I]MIBG given to each patient was determined by weighing and measuring the syringe before and after the [^{125}I]MIBG was injected.

Freshly excised surgical specimens were dispatched (unfixed) to the pathologist and radiopharmacist. Pieces of tissue were cut into 1 cm^3 or smaller fragments, weighed wet, transferred to plastic tubes, and labeled for future cross-reference with histopathology. The tissue samples were counted in an automatic NaI(Tl) well-counter with pre-set energy windows set for ^{125}I. An aliquot of the [^{125}I]MIBG injection solution was taken and serial dilutions were prepared as standards in volumes approximating those of the tissue samples. In order to minimize the effects of self-absorption of the low-energy, ^{125}I emissions, the percent uptake within each specimen was calculated as follows:

$$\text{percent injected dose} = \frac{\text{CPM (tissue specimen)} \times 100}{\text{CPM (injected)}},$$

where CPM (injected) is calculated for each tissue specimen by selecting a standard with a volume approximating that of the tissue specimen and dividing the CPM of the standard by the fraction of the injected dose that the standard represents.

Radiation dose estimates for [^{125}I]MIBG in children have been calculated by the Radiopharmaceutical Internal Dose Information Centre and are presented in Table 1 (personal communication: M. Stabin).

Histopathology

The operative specimens were described and dissected in such a way as to preserve together macroscopically similar pieces of tumor. Representative tissues were fixed in 10% buffered formalin, together with all tissues previously removed for measurement of [^{125}I]MIBG uptake. The material was embedded in paraffin wax and processed routinely. Sections cut at 3 μ were stained with hematoxylin and eosin, the Grimelius method for argyrophil granules, and (when necessary) with other techniques. The slides were read and reported without knowledge of the counting data. The amount of tumor present varied considerably in the different tissue samples, and rough estimates were made of the *extent of intact tumor* in each set of slides. The following three categories were used.

1. ≃ 90%. The sections consisted almost entirely of intact tumor.

2. ≃ 50%. The sections consisted of approximately equal amounts of intact tumor and other tissues (degenerate and/or necrotic material, zones of hemorrhage, calcification, chronic inflammation, fibrosis, residual adrenal and/or renal parenchyma).

TABLE 1
Radiation Dose Estimates for [^{125}I]MIBG in the Pediatric Population

Organ	Estimated radiation dose			
	1 yr old mGy/MBq	5 yr mGy/MBq	10 yr mGy/MBq	15 yr mGy/MBq
Liver	1.2	0.66	0.45	0.29
Spleen	0.97	0.54	0.35	0.23
Thyroid	0.44	0.23	0.11	0.071
Bladder wall	0.36	0.18	0.12	0.08
Bone surfaces	0.27	0.12	0.073	0.043
Adrenals	0.22	0.13	0.092	0.06
Salivary glands*	0.22	0.14	0.12	0.084

*Absorbed fraction for photons with energy greater than 30 keV set to 0.1

3. ≃ 10%. The sections consisted mostly of tissues *other than* intact tumor (see above), with only small focal infiltrates of tumor.

MIBG Scintigraphy

At various stages in the course of their disease each child underwent MIBG scintigraphy with either [^{123}I]MIBG or [^{131}I] MIBG. A negative scan was recorded if there was no focal accumulation of the radiopharmaceutical in the tumor sites.

Table 2 indicates for each patient the isotope and activity of radiopharmaceutical that was administered, and the result of the MIBG scintigram.

RESULTS

The uptake of [^{125}I]MIBG in the seven patients was calculated for all tissue samples as described previously, corrected for radiochemical purity, and expressed as percent injected dose and percent injected dose per gram of tissue. In addition, a relative value was assigned to each tissue sample based on the percent injected dose per gram for a given patient. The findings in each of the seven children follow.

Patient 1. A 10-month-old male, had stage IV neuroblastoma diagnosed 3 mo previously when he presented with enlarged left cervical lymph nodes and slightly raised levels of urinary catecholamines. The lymph nodes contained neuroblastoma. Subsequent staging revealed no other sites of disease. He re-presented with bilateral cervical lymphadenopathy after 2 mo which, following full restaging, was shown to be the only site of disease. Diagnostic [^{123}I]MIBG scan was positive. Enlarged lymph nodes were subsequently removed from both sides of his neck. The results of [^{125}I]MIBG uptake and histopathology are shown in Table 3.

Patient 2. A male age 10 yr 2 mo, had stage IV neuroblastoma diagnosed 19 mo previously when he presented with a large abdominal mass arising from the right adrenal gland and metastases in the left supraclavicular lymph nodes. He had received six courses of modified OPEC chemotherapy (Table 4), followed by complete surgical excision of the adrenal tumor, high dose melphalan, and autologous bone marrow rescue. He remained in complete clinical remission for 1 yr before re-presenting with rising levels of urinary catecholamines and enlarged para-aortic lymph nodes. Diagnostic [^{123}I]MIBG scan was positive. Full re-evaluation showed that the para-aortic nodes were the only site of relapse and they were completely resected. The excised tissues were divided into eight pieces, and the uptake of [^{125}I]MIBG together with the corresponding histopathology are shown in Table 5.

Patient 3. A female aged 2 yr 3 mo, had stage III neuroblastoma. She presented 6 mo previously with a large abdominal mass thought to arise from the right adrenal gland, with no other sites of disease. She was given six courses of modified OPEC chemotherapy. At re-evaluation the tumor was judged to be operable and diagnostic [^{131}I]MIBG scan was positive. At surgery the tumor was found to arise from the lumbar sympathetic chain adhering closely to surrounding structures, and resection was incomplete. The excised tissues were divided into seven pieces and the uptake of [^{125}I]MIBG and the corresponding histopathology are summarized in Table 6.

Patient 4. A male age 3 yr 1 mo, had stage IV neuroblastoma diagnosed 6 mo previously when he presented with a large left-sided adrenal mass, and widespread skeletal metastases involving bone and bone marrow. He was treated with six courses of modified OPEC chemotherapy. He was then reassessed and his primary tumor was thought to be operable. Diagnostic [^{123}I]MIBG scan was positive. The adrenal mass was incompletely excised and details of [^{125}I]MIBG uptake and histopathology are shown in Table 7.

Patient 5. A male aged 12 yr 9 mo had stage IV

TABLE 2
MIBG Scintigraphy Details for the Study Patients

Patient	Isotope	Activity (MBq)	Result
1	^{123}I	75	+*
2	^{123}I	185	+
3	^{131}I	18	+
4	^{123}I	185	+
5	^{123}I	185	−
6	^{123}I	185	+
7	^{123}I	185	−

*+ Indicates visible uptake of MIBG by the tumor.

TABLE 3
[^{125}I]MIBG Uptake In Excised Tissue In Patient 1

Tissue	%ID/ gram	Relative value	Pathology
Spec 1	0.071	100.0	Undifferentiated neuroblastoma present as ≃ 90% of all tissues examined histologically in Samples 1–4; no zones of necrosis or calcification. Some residual *uninvolved* nodal tissue also present.
Spec 2	0.058	81.7	
Spec 3	0.052	73.2	
Spec 4	0.051	71.8	
Spec 5	0.019	26.8	Undifferentiated neuroblastoma present focally (≃10% of tissue examined) in sample 5; also some necrosis and calcification.
Controls			
Spec 6	0.011	15.5	
Spec 7	0.0052	7.3	Uninvolved lymph node
Spec 8	0.0038	5.4	

TABLE 4
Modified OPEC Chemotherapy Protocol

Cyclophosphamide	600 mg/m² i.v. stat Day 1
Vincristine	1.5 mg/m² i.v. stat Day 1 (maximum 2.0 mg)
Cisplatinum	100 mg/m² i.v. Day 2
Etoposide	60 mg/m² i.v. over 1 hr, Days 3, 4 and 5

neuroblastoma diagnosed 2 yr previously when he presented with a mass in the region of the right adrenal gland and metastases in cortical bone and bone marrow. He was treated with six courses of modified OPEC chemotherapy, followed by complete surgical excision of the primary tumor, high dose melphalan, and autologous bone marrow rescue. He remained in complete clinical remission for 1 yr and then re-presented with relapse in the para-aortic lymph nodes. Full re-evaluation showed this to be the only site of relapse and diagnostic [^{123}I]MIBG scan was negative. The lymph nodes were completely excised. [^{125}I]MIBG uptake and histopathology are summarized in Table 8.

Patient 6. A female age 2½ yr, had stage IV neuroblastoma diagnosed 6 mo previously when she presented with a large right-sided abdominal mass arising from the right adrenal gland together with cortical bone disease; there was no bone marrow involvement. She was treated with six courses of modified OPEC chemotherapy. She then underwent full re-evaluation and the primary site was shown to be the only site of remaining disease. Diagnostic [^{123}I]MIBG scan was positive. The right adrenal mass was removed along with the kidney, but the resection was incomplete because of closely adherent tissue. Iodine-125 MIBG uptake and histopathology are shown in Table 9.

Patient 7. Patient 7 was a 4 yr, 8 mo female with a long history of abdominal pain. Physical examination revealed a left-sided abdominal mass, confirmed on ultrasound and CT scan. No metastases were detected. Levels of urinary catecholamines were marginally raised, but all other tumor markers were negative. Diagnostic [^{123}I]MIBG scan was negative. At surgery she was found to have a large retroperitoneal tumor that was completely excised. Iodine-125 MIBG uptake and histopathology are shown in Table 10.

TABLE 5
[^{125}I]MIBG Uptake in Excised Tissue In Patient 2

Tissue	%ID/gram	Relative value	Pathology
Spec 1	0.045	100.0	Undifferentiated neuroblastoma present as ≃ 90% of all tissues examined histologically in samples 1–6. No zones of necrosis or calcification.
Spec 2	0.027	60.0	
Spec 3	0.026	57.8	
Spec 4	0.024	53.3	
Spec 5	0.024	53.3	
Spec 6	0.022	48.9	
Controls			
Spec 7	0.0017	3.8	Uninvolved lymph node
Spec 8	0.0015	3.3	Uninvolved lymph node

TABLE 6
[^{125}I]MIBG Uptake In Excised Tissue in Patient 3

Tissue	%ID/gram	Relative value	Pathology
Spec 1	0.061	100.0	Undifferentiated neuroblastoma present as ≃50% of all tissues examined histologically in samples 1–5; zones of fibrosis and calcification also present with focal chronic inflammation.
Spec 2	0.022	36.1	
Spec 3	0.016	26.2	
Spec 4	0.015	24.6	
Spec 5	0.014	23.0	
Spec 6	0.005	8.2	Undifferentiated neuroblastoma present focally in ≃10% of tissues examined histologically in sample 6; necrosis, calcification and inflammation as previously.
Control			
Spec 7	0.003	4.9	Uninvolved lymph node

The association between tissue uptake of [^{125}I]MIBG and histopathologic appearances in the seven patients is summarized in Table 11 and Figure 1.

DISCUSSION

The potential use of systemically administered radiopharmaceuticals in the treatment of neoplastic disease has attracted wide interest (*10,11*). The theoretic advantages of such therapy include tumor-specific localization and fewer side-effects as a result of the relative sparing of normal tissues. Success is, however, largely determined by a clear identification of the factors that influence tumor dosimetry for the particular disease and patient in question. These factors are a combination of physical and biologic parameters. For many potential therapeutic radionuclides such as ^{131}I and ^{125}I, the physical characteristics are well-documented (*12*). Biologic factors—i.e., tumor-tissue concentration, biologic half-lives, organ distribution—are determined by the chemical form of the radionuclide and the nature and the functional state of the various normal or abnormal target tissues. It is therefore important to measure both the quantitative uptake (percent injected dose per gram of tissue) and the duration of radionuclide activity within test and control tissues. The first of these parameters has been addressed in the present study.

The quantitative uptake of MIBG by individual neuroblastomas may predict the possible therapeutic effect

TABLE 7
[^{125}I]MIBG Uptake in Excised Tissue in Patient 4

Tissue	%ID/ gram	Relative value	Pathology
Spec 1	0.018	100.0	Differentiating ganglioneuroblastoma present in between 10% and 50% of tissues examined histologically in samples 1–3.
Spec 2	0.017	94.4	
Spec 3	0.015	83.3	
Spec 4	0.009	50.0	No intact tumor was seen in samples 4–9.
Spec 5	0.0071	40.1	
Spec 6	0.0070	39.4	Sections from *all* samples (1–9) contained organizing hemorrhage and zones of fibrosis and calcification.
Spec 7	0.0068	37.8	
Spec 8	0.0067	37.2	
Spec 9	0.0034	18.9	
Control			
Spec 10	0.0025	13.9	Uninvolved lymph node

of radiolabeled MIBG although the response will depend critically on the radiosensitivity of these tumors. Deacon et al. (*13*) have shown that individual neuroblastoma cells are highly sensitive when irradiated in vitro, but studies with the established neuroblastoma cell line HX138 indicate that when tumor cells are grown either as spheroids or as xenografts in vivo, they are more radioresistant than single cells. This difference in response may be because of the presence of a significant number of hypoxic tumor cells in these more complex tumor systems, but it may also be the consequence of ill-understood "contact effects".

Accumulation of MIBG by neuroblastomas should, in theory, depend mainly on the neuronal uptake 1

TABLE 8
[^{125}I]MIBG Uptake in Excised Tissue in Patient 5

Tissue	%ID/ gram	Relative value	Pathology
Spec 1	0.03	100.0	Undifferentiated neuroblastoma present as ≃90% of tissues examined histologically in sample 1
Spec 2	0.0065	21.7	
Spec 3	0.0065	21.7	
Spec 4	0.0062	20.7	*No* intact tumor identified in samples 2–10, that contain variable amounts of necrosis, hemorrhage, calcification, and fibrosis.
Spec 5	0.0059	19.7	
Spec 6	0.0057	19.0	
Spec 7	0.0054	18.0	
Spec 8	0.0041	13.7	
Spec 9	0.0039	13.0	
Spec 10	0.0032	10.7	
Control			
Spec 11	0.0011	3.7	Uninvolved lymph node
Spec 12	0.0009	3.0	Uninvolved lymph node
Spec 13	0.0002	0.7	Uninvolved fatty tissue
Spec 14	0.0001	0.3	Uninvolved fatty tissue

TABLE 9
[^{125}I]MIBG Uptake in Excised Tissue in Patient 6

Tissue	%ID/ gram	Relative value	Pathology
Spec 1	0.0048	100.0	Almost totally degenerate tumor. Small foci of residual undifferentiated neuroblastoma are seen in specimen 1. *No* intact tumor seen in samples 2–9. All tissues showed extensive necrosis, calcification and fibrosis.
Spec 2	0.0047	97.9	
Spec 3	0.0046	95.8	
Spec 4	0.0037	77.1	
Spec 5	0.0034	70.8	
Spec 6	0.0019	39.6	
Spec 7	0.0019	39.6	
Spec 8	0.0018	37.5	
Spec 9	0.0013	27.1	

system. This uptake has proved difficult to show in the cell culture system, and has only recently been achieved consistently. Our own efforts to localize MIBG within human tumor cells by autoradiography have been unsuccessful possibly because the amounts of MIBG given to the patients were, for obvious ethical and legal reasons, very small. A further correlation was sought between MIBG accumulation and the presence of argyrophil granules within neuroblastoma cells, demonstrated by the Grimelius stain. No association was found, but alternative methods of demonstrating neurosecretory granules in tissue sections are under investigation. Bomanji et al. (*14*) described an association between MIBG uptake and the numbers of argyrophil neurosecretory granules in a series of tumors consisting mainly of phaeochromocytomas and paragangliomas; a single ganglioneuroblastoma was included.

The relationship between total tumor uptake (mean percent injected dose per gram × tumor weight) and quantitative catecholamine excretion (vanillylmandelic acid [VMA], homovanillic acid [HVA], total metadrenalines and 3 methoxytyramine) was investigated. A correlation was demonstrated between tumor uptake and the urinary excretion of VMA and HVA, but not for total metadrenalines or 3 methoxytyramine. (VMA–n = 5, correlation coefficient (r) = 0.99, $p < 0.001$; HVA–n = 6, correlation coefficient (r) = 0.98, $p < 0.001$). This is of interest since many investigators have

TABLE 10
[^{125}I]MIBG Uptake in Excised Tissue in Patient 7

Tissue	%ID/ gram	Relative value	Pathology
Spec 1	0.0028	100.0	Ganglioneuroma present as ≃90% of all tissues examined histologically in samples 1–4. *No* undifferentiated neuroblastoma identified.
Spec 2	0.0025	89.3	
Spec 3	0.0017	60.7	
Spec 4	0.0017	60.7	

TABLE 11
Summary of [^{125}I]MIBG Uptake and Histopathology

Patient	Mean %ID/g	Relative (mean values)	Range %ID/g (tumor only)	MIBG scan	Pathology
1	0.0502	100.0	0.019–0.071	+	>90% Undifferentiated neuroblastoma
2	0.028	55.8	0.022–0.0448	+	>90% Undifferentiated neuroblastoma
3	0.022	43.8	0.0047–0.061	+	>50% Undifferentiated neuroblastoma
4	0.0099	19.8	0.0034–0.017	+	25% Ganglioneuroblastoma
5	0.0077	15.3	0.0039–0.030	–	<10% Undifferentiated neuroblastoma
6	0.0031	6.2	0.0013–0.0048	+	<10% Undifferentiated neuroblastoma
7	0.0022	4.4	0.0017–0.0028	–	Ganglioneuroma
Controls	0.003	5.8	0.0002–0.011		Uninvolved lymph nodes and/or fibro-fatty tissue

shown that MIBG uptake by tumors, as demonstrated by MIBG scintigraphy, does not appear to correlate with urinary catecholamine excretion.

Patients 1–6 were studied *after* they had received extensive chemotherapy which may have modified the results—for example, by acting preferentially on the undifferentiated tumor cells and (perhaps) affecting MIBG uptake mechanisms. One clear finding in the present study was the variable uptake of [^{125}I]MIBG in individual tumors. Adequate discrimination was, however, achieved between [^{125}I]MIBG uptake by non-neoplastic control tissues compared with tumors from the same patient. There was also a trend for more [^{125}I] MIBG to localize in undifferentiated neuroblastomas compared with differentiating tumors, but the number of cases was small and the estimated volumes of residual tumors were only approximate. It should be noted that in the patient with ganglioneuroma who was studied *before* any therapy was given the relative range was 60–100%, which is a narrower range than that shown for all the other patients, possibly demonstrating the more uniform histopathology of the ganglioneuroma.

If the use of MIBG therapy is intended for small-volume, irregularly outlined tumors, it is suggested that the initial uptake of MIBG is likely to be estimated more accurately using in vitro scintillation counting of excised tissues rather than the gamma camera. Assessment of *anatomic* volume of the tumor by CT scan or ultrasound may differ considerably from the *functional* volume determined by the methods described in the present study. The discrepancy is likely to be particularly large in neuroblastomas treated previously by cytotoxic drugs; such tumors are composed of a heterogeneous mixture of intact and degenerate neoplastic cells of varying differentiation together with the extensive local changes (inflammation, fibrosis, necrosis, calcification) that are associated with chemotherapy. Bone metastases are clearly not amenable to in vitro counting of MIBG uptake, although bone marrow infiltration may be assessed by the methods described here with the added advantage that neuroblastoma cells in bone marrow are more readily quantitated. More accurate measurement of MIBG uptake in the bone marrow is particularly relevant as bone marrow hypoplasia is one of the dose-limiting toxic effects of MIBG treatment.

Preliminary tumor dose estimates based on our biopsy data have been calculated for a range of effective half-lives (T_{eff}) assuming all nonpenetrating radiation is absorbed within the tumor mass and extra-tumor activity contributes no dose. Based on these calculations it seems likely that only certain patients would receive tumor doses >20 Gy given the range 0.11–2.6 Gy/GBq (T_{eff} = 24hr) to 0.45–10.5 Gy/GBq (T_{eff} = 96hr). A more complete estimate of tumor dosimetry is in progress.

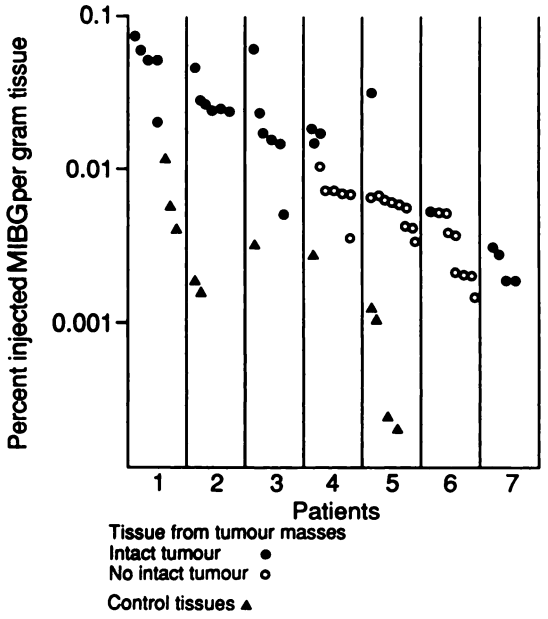

FIGURE 1
Summary of tissue uptake of [^{125}I]MIBG and histopathologic findings. Tumor masses from Patients 1, 2, 3, 5, and 6 contained varying proportions of undifferentiated neuroblastoma. The tumor from Patient 4 was a partly differentiating ganglioneuroblastoma. The tumor from Patient 7 was a ganglioneuroma with no undifferentiated component. See "Results" for further details.

Since dose calculation is essential to plan treatment to maximize effect and to identify patients for whom this expensive therapy is appropriate, we recommend that dose calculation should be performed on excised soft-tissue neuroblastoma prior to MIBG therapy, until gamma camera estimates are shown to be more reliable.

CONCLUSION

A small series of children with neuroblastoma received i.v. [^{125}I]MIBG before major surgery. The uptake of [^{125}I]MIBG was measured quantitatively in the excised tissues by scintillation counting and correlated with histopathology. There was satisfactory discrimination between [^{125}I]MIBG uptake by non-neoplastic control tissues and by tumor. Uptake varied between different tumors and different patients, but there was a trend to greater [^{125}I]MIBG accumulation by the more undifferentiated tumors. Histopathologic appearances may predict MIBG uptake by neuroblastoma and—perhaps—a therapeutic effect with MIBG-targeted radiotherapy.

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