Acute Changes in Blood Pressure in Patients With Neuroblastoma Treated With ^{131}I-Metaiodobenzylguanidine (MIBG)

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Background. Iodine-131-metaiodobenzylguanidine (^{131}I-MIBG) provides targeted radiotherapy for children with neuroblastoma. The aim of our study was to evaluate systematically the acute effects of ^{131}I-MIBG on blood pressure in patients with neuroblastoma and to identify possible predictors of hypertension. **Procedure.** We conducted a retrospective chart review of neuroblastoma patients who were treated with ^{131}I-MIBG between January 1, 1999 and June 1, 2012 at the University of California, San Francisco. Clinical data for 172 patients with neuroblastoma, receiving 218 administrations of ^{131}I-MIBG, were collected. The primary endpoint was development of systolic blood pressure above the 95th percentile for age. Logistic regression with generalized estimating equations to account for multiple administrations in some subjects was used to identify bivariate and multivariate predictors of hypertension. **Results.** Of the 218 administrations of ^{131}I-MIBG, 112 (51.3%) were associated with at least one episode of systolic hypertension during or after the ^{131}I-MIBG infusion. The majority of these acute elevations in blood pressure resolved within 48 hours of the infusion. Only six administrations in five patients required nifedipine administration to lower blood pressure. Younger age ($P = 0.012$), lower eGFR ($P = 0.047$), and elevated blood pressure measurements immediately before infusion began ($P = 0.010$) were all independently associated with risk of treatment-associated hypertension. **Conclusions.** Acute elevations in blood pressure are common after therapeutic doses of ^{131}I-MIBG. Elevations in blood pressure typically occur only within the first 48 hours after ^{131}I-MIBG administration. Blood pressure monitoring during this period of risk is recommended. Pediatr Blood Cancer 2013;60:1424–1430. © 2013 Wiley Periodicals, Inc.

Key words: hypertension; MIBG; neuroblastoma

INTRODUCTION

Neuroblastoma is an embryonal tumor derived from the peripheral sympathetic nervous system. Metastatic disease is present at diagnosis in half of the cases. Despite improvement in outcome with intensification of therapy and treatment of minimal residual disease, 15% of patients with high-risk neuroblastoma have disease that is refractory to induction chemotherapy, and more than 50% of patients who achieve initial remission ultimately relapse and die as a result of their disease [1].

As a tumor derived from the sympathetic nervous system, neuroblastoma cells typically express the norepinephrine transporter. This allows for the active intracellular uptake of radiolabeled metaiodobenzylguanidine (MIBG). MIBG is a guanethidine derivative and analogue of norepinephrine with specific affinity for neural crest tissues. When labeled with iodine-131 (^{131}I-MIBG), MIBG serves as a targeted radiotherapy for children with neuroblastoma, with response rates varying from 25% to 40% [2]. In the largest phase II clinical trial of 164 patients with relapsed disease treated with ^{131}I-MIBG, the response rate for all patients was 36% [3]. ^{131}I-MIBG has predominantly been used as a single agent in relapsed disease. However, ^{131}I-MIBG is increasingly being used as a form of treatment earlier in the course of disease or combined with other agents. With this expanding role in therapy for neuroblastoma, it is essential to develop a greater understanding of the side effects of ^{131}I-MIBG in these patients.

Patients with neuroblastoma may present with hypertension in approximately 10% of cases [4]. However, the specific effect of ^{131}I-MIBG administrations on blood pressure in neuroblastoma patients has not been extensively investigated. Elevated blood pressure during and following ^{131}I-MIBG administration is of particular interest since ^{131}I-MIBG is a norepinephrine analogue that has the potential to mimic the physiologic effects of norepinephrine [5].

The few reports on hypertension following ^{131}I-MIBG therapy have shown varying results. A phase I/II study of ^{131}I-MIBG in neuroblastoma found that 3 of 25 patients developed asymptomatic transient changes in blood pressure between 2 and 4 hours after administration. The changes observed were variable with one patient becoming hypertensive and two hypotensive. No patients required pharmacologic intervention [6]. Another study reported that the majority of infusions were uncomplicated, with blood pressure changes that were not predictable or clinically relevant. However, this group reported four significant adverse events related to hypertension that occurred during or within 1 day after ^{131}I-MIBG administration [7].

We report here a systematic analysis of the effects of ^{131}I-MIBG therapy on blood pressure in patients with neuroblastoma. We examined the relationship between changes in blood pressure during and after treatment with ^{131}I-MIBG and possible risk factors, including both patient specific variables and characteristics of the infusion.

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MATERIALS AND METHODS

Patients and Treatment

This was a retrospective medical record review, approved by the Committee on Human Research of the University of California, San Francisco (UCSF). The clinical records of patients with neuroblastoma treated with ^{131}I-MIBG between January 1, 1999 and June 1, 2012 at UCSF were reviewed. Data for each ^{131}I-MIBG administration were collected. All evaluated patients either failed to achieve partial or complete response following standard induction therapy or developed progressive disease at any time before receiving ^{131}I-MIBG therapy. All patients also demonstrated ^{131}I-MIBG uptake in skeletal or soft tissue sites prior to treatment and were enrolled on therapeutic trials with ^{131}I-MIBG, with appropriate informed consent obtained prior to participation.

Patients were treated on one of nine clinical trials open during the time period covered by this report. These included: a multi-institutional Phase II study of ^{131}I-MIBG [3]; an ongoing UCSF compassionate use protocol of single agent ^{131}I-MIBG; NANT 2004-06—a phase I study of ^{131}I-MIBG with vincristine and 10 days of irinotecan [8]; an ongoing UCSF study of ^{131}I-MIBG with vincristine and 5 days of irinotecan; NANT 99-01—a phase I study of ^{131}I-MIBG with myeloablative chemotherapy [9]; NANT 2001-02—a phase II study of ^{131}I-MIBG with myeolablative chemotherapy; NANT 2000-01—a phase I study of double infusion of ^{131}I-MIBG [10]; NANT 2007-01—a phase I study of no-carrier added ^{131}I-MIBG [11]; and NANT 2007-03—an ongoing phase I study of vorinostat and ^{131}I-MIBG. The ^{131}I-MIBG for the studies was supplied either by DraxImage Radiopharmaceuticals, Nuclear Diagnostic Products, the University of Michigan, or UCSF, except for three patients treated on NANT 2007-01 treated with no-carrier added ^{131}I-MIBG (Azedra) from Molecular Insight Pharmaceuticals, Inc. The specific activity ranged from 26.94 to 51.78 mCi/mg MIBG, except for the three patients who were treated on the NANT 2007-01 study with no-carrier added ^{131}I-MIBG in whom the specific activity was greater than 2,700 mCi/mg MIBG.

Patients were treated with one to three courses of ^{131}I-MIBG. ^{131}I-MIBG was given intravenously over a 1–2 hour period, except for no-carrier added ^{131}I-MIBG which was infused over 30–60 minutes. Hydration, thyroid protection with potassium iodide with or without potassium perchlorate, and a Foley catheter for bladder protection were routinely used. All patients remained in radiation-protected isolation for 3–8 days until radiation emissions declined and met institutional regulations [12].

Outcome Variables

Blood pressure monitoring was performed following UCSF standard practice for patients receiving ^{131}I-MIBG therapy. Blood pressures were typically obtained using automated blood pressure machines equipped with age- and weight-appropriate blood pressure cuffs. A baseline blood pressure measurement was obtained prior to administration, and measurements of the patient's blood pressure were recorded every 15 minutes throughout the ^{131}I-MIBG infusion. Following the completion of the ^{131}I-MIBG administration, blood pressure readings were recorded every 8–12 hours until hospital discharge. If at any time blood pressure measurements were outside of age-appropriate normal ranges, nursing staff typically immediately repeated the blood pressure to confirm the findings.

For the purposes of statistical analysis, blood pressure values were converted into blood pressure percentile values for the given gender, age, and height of each patient. These were taken from percentile charts of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents [13]. The charts contain systolic and diastolic blood pressure values of the 50th, 90th, 95th, and 99th percentile for children between the ages of 1 and 17 years. For the 17 patients older than 17 years of age, blood pressure values were categorized using the US National Heart, Lung and Blood Institute values for normal (<90th percentile), pre-hypertension (90–95th percentile), stage 1 hypertension (95th–99th percentile), and stage 2 hypertension (>99th percentile) [14]. The primary endpoint for statistical analysis was development of systolic hypertension defined as values that fell above the 95th percentile for the patient's age, gender, and height during the ^{131}I-MIBG infusion or following the infusion until hospital discharge. Systolic load was defined as the percentage of systolic blood pressure measurements that fell above the 95th percentile during the hospital stay [15]. In addition, diastolic blood pressure data were collected for secondary descriptive analysis of changes in blood pressure in response to ^{131}I-MIBG therapy. Another secondary endpoint was the maximum relative change in systolic blood pressure from baseline to end of the ^{131}I-MIBG infusion. Systolic blood pressure was chosen as the primary endpoint based on previous work that showed an effect of ^{131}I-MIBG on systolic blood pressure as well as the similar distributions of systolic and diastolic blood pressure changes observed in neuroblastoma patients treated with ^{131}I-MIBG [7].

Predictor Variables

For each administration of ^{131}I-MIBG, information on patient characteristics was extracted from medical records. Demographic variables included patient age at treatment, race, ethnicity, weight, height, body mass index category (normal, overweight, or obese according to the internationally recognized thresholds defined by the Institute of Child Health, London [16]). Additional baseline variables included level of urine catecholamines and history of hypertension, renal disease, or nephrectomy. Glomerular filtration rate was estimated (eGFR) from serum creatinine obtained prior to ^{131}I-MIBG infusion. Patients 16 years of age and younger had eGFRs determined using the estimated bedside GFR calculations of $0.413 \times$ (height in cm/serum creatinine), which is a modified form of the original Schwartz formula [17]. Patients with creatinine measurements taken before February 2010 were adjusted by 0.09 mg/dl to account for a systemic change in lab creatinine assays made following that date. Patients 17 years old and over had eGFRs calculated using the Modification of Diet in Renal Disease (MDRD) equation, which calculates eGFR based on age, blood urea nitrogen concentration, serum creatinine concentration, albumin levels, gender, and race [18]. Variables associated with the ^{131}I-MIBG infusion itself were also collected, including length of infusion (minutes), rate of infusion (mCi/kg/minutes), and specific activity of MIBG (mCi/mg).

Statistical Analysis

We performed descriptive analyses of changes in blood pressure values during and after each ^{131}I-MIBG administration, including the incidence of our primary endpoint of systolic hypertension. We

performed bivariate analyses using logistic regression models to assess associations between systolic hypertension and potential predictive clinical factors. A generalized estimating equations (GEE) approach was used in order to account for possible intrapatient correlation for subjects who received more than one ^{131}I-MIBG administration. Similarly, we performed multivariate logistic regression with GEE to assess the independent impact of potential predictor variables. All analyses were performed using Stata 10.1.

RESULTS

Patient Characteristics

A total of 172 patients received 218 administrations of ^{131}I-MIBG (Table I). Of these, 205 had blood pressure data available before, during, and after the ^{131}I-MIBG infusion. In 13 administrations, blood pressure measurements during the infusion were missing. These administrations were included in the analysis since blood pressure data following the infusion were available.

The majority of the patients were boys, accounting for 143 administrations. The mean age was 9.9 years (range 1–40 years). Very few patients had pre-existing hypertension, underlying renal disease, or prior nephrectomy. Seven patients had been diagnosed with hypertension before ^{131}I-MIBG therapy, and five of those patients were prescribed anti-hypertension medications. Six patients had underlying renal disease, including atrophy of a kidney, decreased kidney function, renal tubular wasting, obstruction of a kidney, and hydronephrosis. Thirteen patients had a prior nephrectomy during resection of the original tumor. Only one patient had both known renal disease (an atrophic left kidney) and pre-existing hypertension prior to ^{131}I-MIBG therapy, but was not being treated with anti-hypertension medication at the time of infusion.

TABLE I. Demographic and Clinical Characteristics of 172 Patients With Neuroblastoma Receiving 218 Administrations of ^{131}I-MIBG

Characteristics	All administrations (n=218)	SBP <95% throughout stay (n=106)	SBP >95% during or post-infusion (n=112)	P-value
Age at study entry (years)	9.9±7.1	12.0±7.9	7.9±5.6	0.001
Gender				0.517
Males	143	72	71	
Females	75	34	41	
Ethnicity				0.81
Hispanic or latino	28	13	15	
Not hispanic or latino	190	93	97	
Race				0.921
American Indian or Alaskan Native	1	1	0	
Asian	25	14	11	
Native Hawaiian or Pacific Islander	4	2	2	
Black/African American	9	5	4	
White; More than one race	149	69	80	
Unknown	30	15	15	
Relapsed vs. refractory				0.204
Relapsed disease	111	59	52	
Refractory disease	107	47	60	
Urine catecholamines (VMA and/or HVA)				0.177
Elevated	78	34	44	
Normal	48	27	21	
eGFR (ml/minutes/1.73m^2)	134.9±44.5	140.0±49.6	130.2±38.8	0.14
History of hypertension				0.1
History of hypertension	7	1	6	
No history	211	105	106	
SBP before administration				0.003
<95th centile	199	104	95	
>95th centile	19	2	17	
Chronic anti-hypertension medications				0.226
Chronic anti-hypertension medications	5	1	4	
No medications	213	105	108	
Nephrectomy				0.39
Nephrectomy	18	7	11	
No nephrectomy	200	99	101	
Overweight by body mass index category				0.744
Overweight	37	17	20	
Not overweight	181	89	92	
Obese by body mass index category				0.289
Obese	12	8	4	
Not obese	206	98	108	

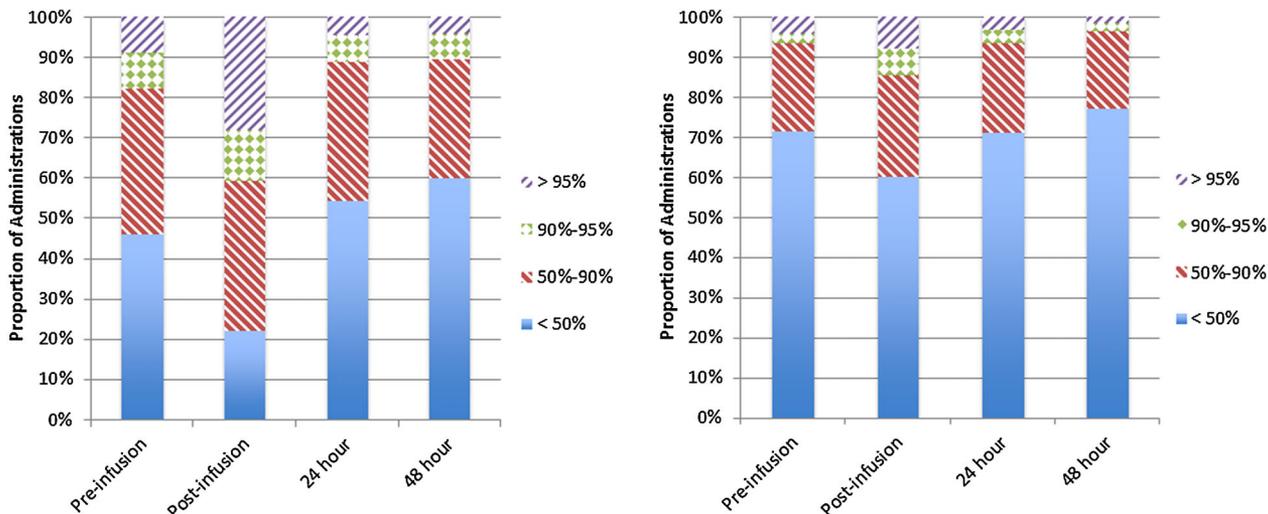For continuous variables, the mean and standard deviation are provided.

Fig. 1. Systolic (**A**) and diastolic (**B**) blood pressure percentile distribution before, immediately after, 24 hours after, and 48 hours after ^{131}I-MIBG administration. BP measurements divided into one of four BP percentile categories (>95th percentile, 90th–95th percentile, 50th–90th percentile, <50th percentile).

Incidence and Extent of Systolic Blood Pressure Elevations

Figure 1A displays the distribution of systolic blood pressure percentiles before, during, and within the first 48 hours after ^{131}I-MIBG infusion, the period during which most blood pressure changes occurred. 8.7% of administrations had systolic hypertension (SBP >95% for age and height) at baseline prior to ^{131}I-MIBG infusion. Immediately following the ^{131}I-MIBG infusion, 27.9% of administrations had systolic systolic blood pressures >95th percentile. Less than 10% of administrations were associated with systolic blood pressures >95th percentile by 24 and 48 hours after ^{131}I-MIBG infusion. Overall, 112 of the 218 administrations were associated with at least one episode of systolic blood pressure >95th percentile during or after ^{131}I-MIBG infusion for an incidence of 51.3%. Nifedipine was administered to lower blood pressure during six administrations of ^{131}I-MIBG in five patients.

An increase in the proportion of patients with elevated diastolic blood pressure measurements after the ^{131}I-MIBG infusion was also observed, but to a lesser degree (Fig. 1B). Prior to therapy, nine administrations (4.1%) in nine patients had diastolic blood pressure measurements >95th percentile. The number of administrations with elevated diastolic blood pressure values increased to 17 (7.8%) immediately after the ^{131}I-MIBG infusion. Similar to systolic blood pressure measurements, the number of administrations with hypertensive diastolic blood pressure measurements decreased by 24 and 48 hours after ^{131}I-MIBG infusion.

The mean absolute systolic blood pressure change seen immediately after completion of ^{131}I-MIBG administrations was an increase of 8.5 mmHg. The mean absolute diastolic blood pressure increase immediately after infusion was 3.9 mmHg. By 24 hours after the infusion, the mean absolute systolic blood pressure change was a decrease of 3.8 mmHg from baseline and the mean absolute diastolic blood pressure change was a decrease of 0.2 mmHg from baseline. Figure 2 shows the maximum relative change in systolic blood pressure during or immediately at the completion of each ^{131}I-MIBG administration. Of the 218

administrations, 182 administrations had elevated systolic blood pressure measurements of any degree either during or immediately after the completion of infusion.

Figure 3 displays the burden of systolic hypertension (systolic load) over the course of each ^{131}I-MIBG hospitalization. The average number of available blood pressure measurements for each patient over the course of each admission was 18 (range 9–48). One hundred four administrations had no episodes of systolic blood pressure >95th percentile during the hospitalization. 65 administrations had 1–20% of their systolic blood pressure measurements >95th percentile. Thirty administrations had 21–40% of their systolic blood pressure measurements >95th percentile, and only
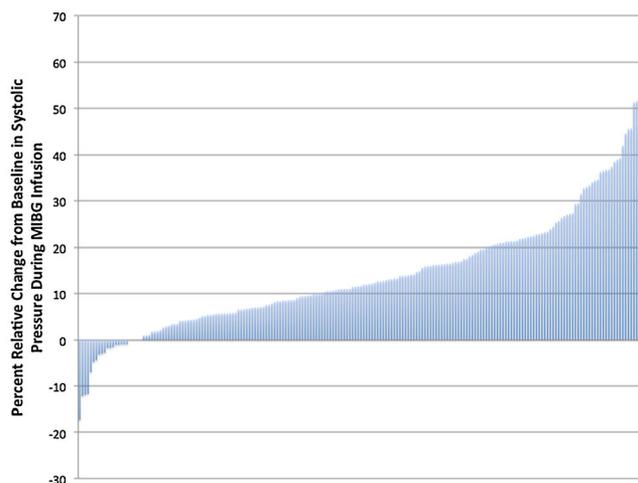

Fig. 2. Maximum percent relative change from baseline in systolic blood pressure during or immediately after ^{131}I-MIBG administration of each individual patient; N = 205, median change in systolic blood pressure is 14.4%. Thirteen patients without systolic blood pressure data during or immediately after ^{131}I-MIBG administration were removed.
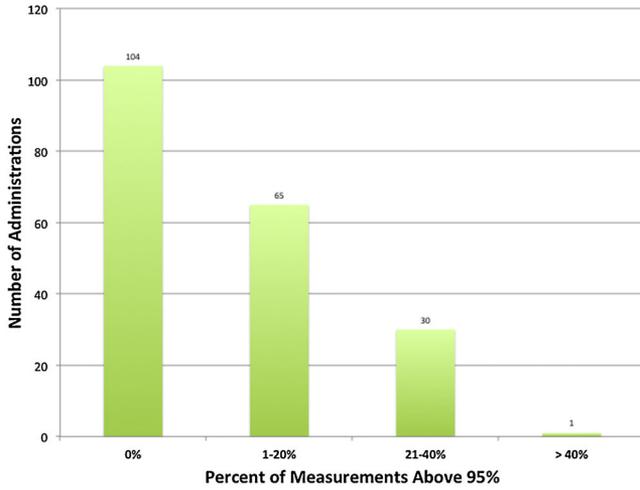
Fig. 3. Percent of systolic blood pressure measurements falling above the 95th percentile for age throughout hospitalization in 200 administrations (18 patients that had systolic BP measurements >95th percentile before infusion began were excluded).

one administration exhibited systolic blood pressure measurements >95th percentile for over 40% of the measurements.

Predictors of ^{131}I-MIBG Associated Elevations in Systolic Blood Pressure

Table I shows bivariate associations between patient demographic or clinical characteristics and the development of systolic blood pressure >95th percentile. Younger patients had a significantly higher risk of developing systolic blood pressure >95th percentile ($P = 0.001$). A significant association was also observed between systolic blood pressure >95th percentile during or after the infusion and having an elevated blood pressure measurement above the 95th percentile prior to the infusion ($P = 0.003$). A suggestive association ($P = 0.14$) was observed between systolic blood pressure >95th percentile and the eGFR (ml/minutes/1.73 m^2).

Table II shows the effect of dose of ^{131}I-MIBG administered and rate of the infusion of ^{131}I-MIBG on systolic blood pressure. Based on the bivariate analysis, lower absolute doses of ^{131}I-MIBG appeared to have a significant positive association with elevated blood pressure. This observation is potentially confounded by the aforementioned association with young age. Consistent with that possibility, the dose of ^{131}I-MIBG per kilogram of body weight was not associated with the risk of hypertension. The rate of ^{131}I-MIBG infusion in mCi/kg/minute was also not associated with risk of systolic hypertension. As with absolute activity infused, the absolute amount of MIBG in mg correlated was inversely correlated with the development of systolic blood pressure >95th percentile, though this effect was not seen in evaluating the mg of MIBG per kilogram of body weight. Likewise, the rate of infusion in mg/kg/minutes did not correlate with development of systolic blood pressure elevation. Absolute duration of infusion in minutes also did not correlate with development of systolic blood pressure elevation.

Table III shows the results of multivariate logistic regression models of potential predictors of systolic blood pressure >95th percentile during or after ^{131}I-MIBG administration. Variables

TABLE II. Effect of ^{131}I-MIBG Dose and Dose Rate on Systolic Blood Pressures (SBP) During or After ^{131}I-MIBG Infusion

	Total dose (mCi) (P=0.003)		Total dose (mg) (P=0.049)		Dose/kg (mCi/kg) (P=0.66)		Dose/kg (mg/kg) (P=0.40)		Total time (minutes) (P=0.56)		mCi/kg/ minutes (P=0.2)		mCi/minutes (P=0.04)		mg MIBG/kg/ minutes (P=0.135)		mg MIBG/ minutes (P=0.24)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
All administrations	470	263	13.94	7.54	15.0	3.9	0.46	0.15	109	21	0.14	0.05	4.5	2.7	0.004	0.0015	0.13	0.08
SBP <95th percentile	532	267	15.17	6.97	14.9	4.0	0.45	0.15	110	19	0.14	0.04	5.0	2.6	0.004	0.0014	0.14	0.07
SBP >95th percentile	411	245	12.81	7.90	15.1	3.8	0.46	0.14	108	23	0.14	0.05	4.0	2.8	0.004	0.0015	0.12	0.09

TABLE III. Multivariate Analysis of Predictive Factors for Hypertension Observed During or After ^{131}I-MIBG Infusion

Associations	Odds ratio (bivariate)	95% confidence interval (bivariate)	Odds ratio (multivariate)	95% confidence interval (multivariate)	P-value (multivariate)
Total dose (mCi MIBG)	0.998	0.997–0.999	1.000	0.999–1.002	0.723
Age	0.907	0.857–0.959	0.913	0.850–0.980	0.012
eGFR (ml/minutes/1.73m^2)	0.994	0.987–1.000	0.993	0.986–0.999	0.047
Elevated BP >95% before RX	9.305	2.121–40.823	6.043	1.525–23.938	0.010

associated with increased odds for blood pressure elevation were younger age ($P = 0.012$), lower eGFR ($P = 0.047$), and elevated blood pressure measurement pretreatment ($P = 0.010$). Total absolute dose of ^{131}I-MIBG was no longer significant. Older patients had decreased odds of having systolic blood pressure >95th percentile, with each additional year of age associated with an odds ratio of 0.91 (95% confidence interval 0.85–0.98) compared to younger patients. Patients with higher eGFR had decreased odds of having systolic blood pressure >95th percentile, with each unit increase in eGFR associated with an odds ratio of 0.99 (95% confidence interval 0.98–0.99) compared to lower eGFR. The odds ratio for patients with blood pressure measurements >95th percentile immediately before the infusion was 6.04 (95% confidence interval 1.53–23.94) compared to patients who were normotensive at the start of the infusion.

DISCUSSION

This retrospective study of 218 administrations of ^{131}I-MIBG therapy in 172 patients provides a comprehensive evaluation of the risk of hypertension after ^{131}I-MIBG therapy for neuroblastoma. We observed systolic blood pressures >95th percentile in 112 administrations. A majority of the elevations in blood pressure were observed during the 2-hour infusion of ^{131}I-MIBG. Only seven of the 112 administrations that experienced systolic blood pressure measurements above the 95th percentile had persistent elevated blood pressure beyond 2 days following administration. In addition, only one administration was associated with systolic blood pressures >95th percentile for more than 40% of blood pressure measurements during the hospital stay. None of the patients experienced life-threatening complications or adverse events from changes in blood pressure, with nifedipine utilized in only 2.8% of administrations.

These findings are in contrast to a previous study that examined the effects of ^{131}I-MIBG therapy on hypertension in 110 administrations. In that study, four adverse events associated with hypertension were observed, including hypertensive encephalopathy and generalized seizures, headaches, and dizziness. All of the adverse events required medical interventions and were observed within 20–25 hours following treatment. Of note, ^{131}I-MIBG was typically infused in less than 60 minutes by that group. Other findings from that study were similar to the observations reported here, most notably that the majority of administrations of ^{131}I-MIBG are generally uncomplicated by hypertension [7].

We examined the effect of various predictive variables and clinical factors on changes in blood pressure measurement following administration of ^{131}I-MIBG. Those that proved to have a significant correlation included age, eGFR prior to therapy, and elevated pretreatment blood pressure measurements. First,

younger patients were more likely to have hypertension compared to older patients. This difference between age groups is unrelated to the dosing of ^{131}I-MIBG each patient received. The younger patients did receive lower amounts of ^{131}I-MIBG in millicuries (mCi), but relative to their weight both old and young patients were given the same dosage of ^{131}I-MIBG in millicuries/kilogram (mCi/kg). Instead, it is possible that this difference may be related to the severity or extent of the disease. Younger patients may have a greater disease burden, as they present with a higher incidence of *MYCN* amplification. It is also possible that younger patients are more sensitive to the adrenergic effect of ^{131}I-MIBG. Finally, the difference in blood pressure changes seen between age groups may simply be a result of greater level of anxiety experienced by younger children compared to older children while admitted to the hospital and separated from their parents for radiation isolation. However, the fact that younger age remained statistically significant even after controlling for baseline hypertension at the start of the infusion argues against this possibility.

We also found that eGFR was significantly associated with elevated blood pressure measurements in bivariate and multivariate analyses. Patients with lower calculated eGFR had an increased risk of having hypertension during or shortly after receiving ^{131}I-MIBG. Reduced eGFR is known to be associated with hypertension, and thus this increased risk of hypertension post-MIBG infusion may be a manifestation of the known effect of reduced renal function on blood pressure [19]. In addition, the clearance of radiolabeled MIBG in children with neuroblastoma occurs mainly through urinary excretion. A lower eGFR may reflect reduced renal clearance of radiolabeled MIBG. As a result, patients with lower eGFR may have had greater exposure to ^{131}I-MIBG leading to greater risk of hypertension.

The other predictive factor found to be significant for hypertension following administration of ^{131}I-MIBG was elevated blood pressure measurements prior to the start of the infusion. It is possible that elevated pre-infusion blood pressure measurements represent true hypertension and blood pressure elevations post-infusion in these patients reflect further increase in blood pressure and worsening hypertension related to medication infusion. Alternatively, the elevation in blood pressure seen in these patients post-infusion may have been unrelated to the medication the patients receive but rather were the natural variation of their already elevated blood pressure. It may also be that high blood pressure measurements prior to infusion serve as an indication of an overall increased level of anxiety within a given patient, resulting in an elevated baseline blood pressure. The increased blood pressure level then continues throughout the administration of therapy until the child is able to relax, allowing his or her blood pressure to return to normal levels.

While this study is a comprehensive evaluation of hypertension after ^{131}I-MIBG therapy for neuroblastoma, there are additional

areas worthy of further study. This includes an analysis of the severity of disease as a possible risk factor for increased blood pressure measurements following ^{131}I-MIBG therapy. The level of disease burden could be measured based on whether or not the patient exhibited MYCN amplification as well as the extent of involvement of disease. In addition, many neuroblastoma patients receive multiple administrations of ^{131}I-MIBG therapy but the exact effect of repeated infusions on blood pressure is not explored within the current study. Lastly, a prospective study on the level of serum catecholamines immediately before and after administration of ^{131}I-MIBG may be informative. Such a study may provide some insight on whether the therapy is leading to a direct fluctuation of catecholamine levels, which is then resulting in changes in blood pressure.

In conclusion, therapeutic doses of ^{131}I-MIBG led to systolic blood pressures >95th percentile in approximately half of the administrations. These hypertensive episodes were transient and typically occur only within the first 48 hours after ^{131}I-MIBG administration. Blood pressure monitoring during this period of risk is recommended, though intervention with antihypertensive medications was only rarely required.

ACKNOWLEDGMENTS

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