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The Role of Radiopharmaceuticals MIBG and (V) DMSA in the Diagnosis of Medullary Thyroid Carcinoma

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The diagnostic value of $^{123/131}$I meta-iodo-benzylguanidine (MIBG) and ^{99m}Tc (V) dimercaptosuccinic acid (DMSA) was investigated in 12 patients with proven medullary thyroid carcinoma (MTC). Scintigraphic imaging with DMSA was negative in nine of 12 patients. Scintigraphy with MIBG was positive in only one case. In proven primary or recurrent disease, DMSA sensitivity was 50% and MIBG sensitivity was 25%. Such sensitivities become much lower in subjects with high calcitonin (CT) levels who have had negative surgical explorations: DMSA 17% and MIBG 0%. DMSA detected tumor in 25% of the patients and MIBG in only 8%. The positivity of these scintigraphies appears to be unrelated to carcinoembryonic antigen and CT plasma levels. Such data suggest that scintigraphies with MIBG and DMSA are only modestly useful in the diagnosis of MTC. (Henry Ford Hosp Med J 1989;37:175-7)

In the follow-up of patients treated by total thyroidectomy for medullary thyroid carcinoma (MTC), the presence of high baseline calcitonin (CT) levels and/or remarkably increased CT levels after calcium or pentagastrin infusion represent evidence of recurrent disease. The tumor may metastasize locally or to bones and soft tissue (1); such metastases are difficult to detect with the commonly available techniques. To localize tumor recurrence, various imaging methods have been used, including ultrasound and axial computed tomography. Several reports have suggested a potential diagnostic and therapeutic role of ^{131}I meta-iodo-benzylguanidine (MIBG) in MTC (2). The radioiodinated MIBG uptake in MTC is not surprising because C-cells originate from the ectodermal neural crest as do many of the other neoplasms imaged with this agent. The most encouraging results seem to be offered by ^{99m}Tc (V) dimercaptosuccinic acid (DMSA) which accumulates in the tumor and metastatic sites. Nevertheless, several authors report conflicting data (3,4). To gain further knowledge regarding the use of MIBG and DMSA, we investigated a group of 12 patients with histologically proven MTC.

Methods

Patients

Twelve patients, four females and eight males aged 11 to 67, were studied. Five patients belonged to two multiple endocrine neoplasia type 2A (MEN 2A) families and seven had sporadic MTC. Of the 11 patients with elevated basal plasma CT levels, ten had previously undergone total thyroidectomy and lymphadenectomy and one was studied both before and after partial ablation of the neoplastic masses in the neck. The twelfth patient, a member of a MEN 2A family, had not yet had total thyroidectomy and showed high CT serum levels only after calcium and pentagastrin stimulation. Nine of the 12 subjects also showed elevated carcinoembryonic antigen (CEA) levels.

CT and CEA measurement

The quantitative determination of CT in serum was measured using a radioimmunologic method (RIA-mat Calcitonin II, Byk-Santec Diagnostica Dietzenbach, RFA). CEA values were defined using a monoclonal radioimmunologic method (Ammerwell CEA Assay monoclonal Amersham). The normal values were below 150 pg/mL for serum CT levels and below 5 ng/mL for plasma CEA levels.

MIBG

MIBG scintigraphies were performed after an intravenous injection of 90 MBq of ^{131}I MIBG or 185 MBq of ^{123}I MIBG. Imaging with ^{131}I MIBG was performed at 24 and 48 hours and with ^{123}I MIBG at 4 and 24 hours after. All patients received blocking doses of Lugol's iodine solution orally (60 mg potassium iodide twice daily beginning two days before the start of the study and continuing throughout its duration).

DMSA

Two commercial kits of Tc (V) DMSA were obtained using controlled alkalination of the Tc(III) DMSA mixture commonly

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Table
Comparison Between (V) DMSA, MIBG, and Other Investigations

Patient	Age (years)	Diagnosis	Total Thyroidectomy	CEA*	CT* Basal	CT* Stimulated	Other Investigations	DMSA	MIBG
1	63	S/P	–	9.9	>1000		+	+†	+†
2	29	M/R	+	>60	475		+	–	–
3	24	S/R	+	>60	>1000		+	+	–
4	50	S/R	+	>60	>1000		+	–	–
5	12	M/P	–	2.2	51	>1000	+‡	–	–
6	46	S/R	+	4.0	409		–	–	–
7	29	M/R	+	17.2	200		–	–	–
8	68	S/R	+	>60	>1000		–	–	–
9	65	S/R	+	7.2	223		+‡	+	–
10	42	S/R	+	11.0	274		–	–	–
11	19	M/R	+	>60	410		–	–	–
12	20	M/R	+	0.9	258		–	–	–

*For normal values see text.
†Maintained positivity after partial ablation of tumor mass.
‡After scintigraphy investigation.
S = sporadic, M = MEN 2A, P = primary tumor, R = recurrent disease.

used for kidney scanning. DMSA scintigraphies were performed two to three hours after an intravenous administration of 370 to 444 MBq of ^{99m}Tc (V) DMSA. Quality control of ^{99m}Tc (V) DMSA at the time of preparation ensured that the material administered was alkaline (pH 8 to 8.5).

These scintigraphies were performed using a large field of view gamma camera with high resolution collimator interfaced to a data processor. The two types of scintigraphies were performed within a one-month period.

Results

Nine of 12 scintigraphic imagings with DMSA gave negative responses, while scintigraphy with MIBG was positive in only one case (Table). Both DMSA and MIBG gave positive responses only in the patient with the primary tumor. This patient had a large mass in the neck area which was positive to scintigraphy with both tracers before and after partial ablation. The two subjects who were positive with DMSA but not with MIBG had recurrent disease, one with histologically positive lateral cervical lymph nodes and one with uptake in the tenth left rib and skull. Computed axial tomography confirmed the presence of a rib lesion. Two of the nine subjects with negative responses to DMSA and MIBG had histologically positive lateral cervical masses; one was the only patient who showed an accumulation in the renal areas. A third subject had two intrathyroid neoplastic foci. The positivity of these scintigraphies did not correlate with CEA and CT plasma levels.

Discussion

The diagnosis of MTC recurrence is based on the assay of plasma CT and CEA levels because high CT levels are known to be related to residual tumor or recurrences (5) and elevated plasma CEA levels often indicate more aggressive tumors (6). However, traditional imaging techniques do not have high sensitivity in localizing residual tumor. Scanning with ^{99m}Tc (V) DMSA and ^{131}I MIBG has been proposed. MIBG, an analog of the adrenergic blocking agent, has been used for the localization of pheochromocytoma and may accumulate in MTC as well (7). The mechanism of (V) DMSA concentration in neoplastic sites is not clear. The nonspecific accumulation of this radiotracer in the neoplastic sites may be related to local abnormalities of phosphorus and calcium metabolism (8). Most reports show a much lower diagnostic efficacy for MIBG in comparison with DMSA (9). However, MIBG has a potential therapeutic role in MTC (10).

Guerra et al (11), reporting the data available in literature, showed that DMSA sensitivity is about 80% for primary tumors and 68% for recurrent diseases. Although these data seem encouraging, the investigations have mainly involved subjects with tumoral lesions already evident. In the 12 subjects of our study, one true positive was observed with MIBG, three true positives with DMSA, and no false-positives. Other investigations identified tumoral lesions in six of the 12 patients. By considering only those patients who presented with primary tumors or recurrent disease already proven at the time of scintigraphic investigation (patients 1 to 4), DMSA sensitivity is 50% (or 66% not considering patient 2 with tracer kidney uptake) and MIBG sensitivity is 25%. Such sensitivities are much lower when considering those subjects with high CT levels and other negative investigation (all 12 subjects): DMSA 25% and MIBG 8%. In subjects with high CT levels and negative explorations (patients 5 to 12), DMSA sensitivity is about 17% and MIBG 0%.

Our data show that DMSA and MIBG scintigraphies can efficaciously identify tumor lesions that are already evident and have a much lower sensitivity when such lesions are not obvious. These scintigraphic approaches are of only modest utility in the postoperative follow-up of MTC patients. However, MIBG is useful in the diagnosis of pheochromocytoma (12) and has a potential therapeutic role in MTC. A radioiodinated analog of sandostatin (^{123}I-labeled tyr-3-octreoite) has been

recently investigated to label somatostatin receptors in endocrine-related tumors in vivo and to localize tumors that present membrane-bound somatostatin receptors (13).

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