DIAGNOSTIC NUCLEAR MEDICINE

Salivary Gland Accumulation of Meta-[^{131}I]Iodobenzylguanidine

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Intense uptake of *m*-[^{131}I]iodobenzylguanidine (I-131 MIBG) has been observed in the salivary glands of patients undergoing scintigraphy for the location of suspected pheochromocytomas. This uptake of radioactivity was not due to free I-131 derived from the I-131 MIBG but rather to uptake of I-131 MIBG by sympathetic neuronal elements in the salivary glands. In keeping with this, administration of tricyclic antidepressants reversibly blocked salivary uptake of I-131 MIBG. Furthermore, I-131 MIBG uptake was markedly diminished by the ipsilateral salivary glands in a patient with Horner's syndrome, and was bilaterally diminished in a patient with severe idiopathic sympathetic autonomic neuropathy. The salivary gland uptake of I-131 MIBG may provide a means for the study of sympathetic innervation of these organs, and thus for the study of generalized disorders of autonomic innervation.

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Meta-[I-131]iodobenzylguanidine (I-131 MIBG) is a radiolabeled analog of the adrenergic blocking agent guanethidine (*1*). Its affinity for the adrenal medulla has made it useful in the detection of pheochromocytomas and adrenal medullary hyperplasia (*2,3*). In the canine adrenal medulla I-131 MIBG is sequestered mainly in the chromaffin storage granules (*4*). In addition it appears that a major component of MIBG retained in myocardium is that sequestered within the norepinephrine storage vesicles of the adrenergic nerves of the canine heart (*5*). I-131 MIBG is thus believed to share uptake and storage mechanisms similar to those of norepinephrine.

We have frequently observed prominent visualization of the salivary glands on the I-131 MIBG head-chest images routinely obtained to detect extraadrenal and metastatic pheochromocytomas (*6*). Accumulation of I-131 MIBG in the salivary gland may be related to sympathetic innervation as this organ which, like the heart, is richly supplied by sympathetic nerves (*7,8*). This study was undertaken to elucidate the uptake and excretion mechanism of I-131 MIBG accumulation in the salivary glands.

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MATERIALS AND METHODS

Because the salivary glands are known to concentrate I-131 ions, it was first necessary to exclude the possibility that the observed salivary images were merely due to the uptake of free radioiodide present in the radiopharmaceutical or liberated from it in vivo. To do so, the following experiments were performed.

Studies in man. 1. As the salivary glands, thyroid, and stomach are all known to concentrate iodide (*9*) the frequency of visualization of these organs was evaluated in the images of 151 patients referred for the location of possible pheochromocytomas (67 male; 84 female, ages 6–73 yr).

2. The influence of the dose of iodide administered was noted on the frequency of visualization of salivary glands, thyroid, and stomach. Seventy-five patients had received three drops of saturated solution of potassium iodide per day (SSKI, 120 mg of iodide), 61 had received Lugol's solution six drops per day (40 mg of iodide) to block thyroidal uptake of I-131. Administration of iodides was begun on the day before tracer injection and

continued for at least 4 days afterwards. The remaining 15 patients received no iodides, either inadvertently or because of previous thyroidectomy. The images were obtained at 4 hr in some cases and at 24 and/or 48 hr after the intravenous injection 0.5 mCi of I-131 MIBG per 1.7 m^2 (*2*). Visualization of the salivary glands (parotid) and thyroid were evaluated on the posterior head/chest images. In selected cases, additional anterior and lateral images of the head and neck were obtained for detailed delineation of all the salivary glands. The region of the stomach was examined on anterior and posterior abdominal images.

Studies in the dog. As the dog parotid gland is able to concentrate iodides and the submandibular gland is not (*10,11*), this animal provides an opportunity to determine whether salivary gland activity is due to the uptake of free I-131 ions by acinar tissue or I-131 MIBG by neuronal elements. To do this, tissue distribution studies were performed on three female mongrel dogs (21–27 kg) that were injected with 200 μCi of I-131 MIBG intravenously. No iodides were administered and animals were killed by intravenous sodium pentobarbital 2 hr after tracer injection. Duplicate tissue samples of submandibular and parotid gland were weighed and counted in an auto-gamma counter, with corrections for radioactive decay, background, and counter efficiency. The tissue concentration was expressed as % kg dose/g.

To further elucidate the mechanism of I-131 MIBG uptake, a detailed retrospective examination was made of the group of patients (seven) in whom the salivary glands were not visualized. This included four patients taking tricyclic antidepressant medications, one with profound sympathetic autonomic neuropathy, and one case of unilateral decreased I-131 MIBG uptake in the ipsilateral salivary glands of a woman with Horner's syndrome.

Additional studies were performed to determine whether the radioactivity visualized in the salivary glands at scintigraphy was excreted in the saliva and, if so, in what chemical form.

Salivary gland concentration. The subjects were nine patients with no evidence of salivary gland disorders who were referred for I-131 MIBG imaging (three male, six female, ages 26–66 yr). All subjects received SSKI as described above. After obtaining informed consent, blood samples and unstimulated mixed saliva were collected at 15 min, and at 1, 4, 24, and 48 hr following the injection of the diagnostic dose of I-131 MIBG. Plasma and saliva samples were counted in an auto-gamma counter, with corrections for radioactive decay, background, and counter efficiency. Saliva-to-plasma I-131 ratios were calculated.

Chemical forms of the radioactivity in saliva. The subject was a 61-yr-old white man with metastatic pheochromocytoma, who was referred for I-131 MIBG therapy to his malignant lesions (*12*). The unstimulated mixed saliva was collected 1 hr after completion of an i.v. infusion (over 90 min) of 100 mCi I-131 MIBG. After collection of the unstimulated saliva, a collection was also made following stimulation of the salivary glands by sugarless chewing gum. The chemical form of the radioactivity in the both unstimulated and stimulated saliva was determined using thin-layer chromatography (silica gel G support, acetate/ethanol (1:1) R_f I-131 MIBG = 0.1, R_f I-131 iodide = 0.6) following the dilution of the saliva samples.

RESULTS

Table 1 shows the frequency of visualization of the salivary glands, thyroid, and stomach observed on I-131 MIBG scintigrams. The salivary glands are visualized in 92% to 100% of patients, whereas gastric uptake was never observed despite the fact that both organs share similar mechanisms for the uptake of iodide. The thyroid gland was seen in all instances where iodide treatment was omitted, and in no more than 7% where iodides were administered. The presence or absence of pheochromocytoma did not appear to affect visualization of any of these organs. Figure 1 shows the salivary glands in the presence of SSKI administration.

TABLE 1. VISUALIZATION RATE (PERCENT) OF THE SALIVARY GLANDS, THYROIDS, AND STOMACH on I-131 MIBG IMAGES

	Thyroid blocking agents (dose/day)								
	SSKI (120 mg of I)			Lugol's solution (40 mg of I)			Omitted		
Organs	4 hr	24 hr	48 hr	4 hr	24 hr	48 hr	4 hr	24 hr	48 hr
Salivary gland	100	100	92	—	100	100	—	100	92
Thyroid	0	0	1	—	3	7	—	100*	100*
Stomach	0	0	0	0	0	0	0	0	0
Number of patients	1(1)†	34(5)	76(9)	5(2)	36(12)	44(15)	1	9	13(1)

* Percent in the patients with thyroids (n = 3 at 24 hr, 4 at 48 hr).

† ( ) = number harboring pheochromocytomas.

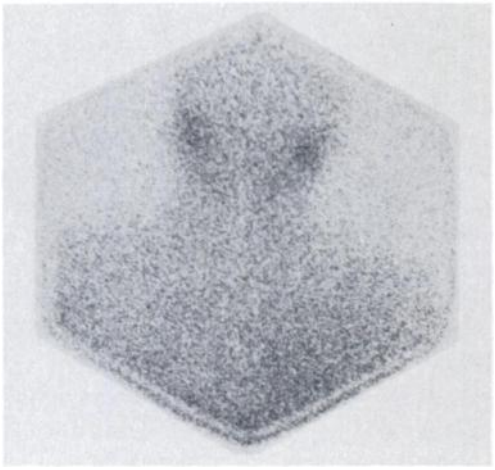

FIG. 1. Posterior head-chest image of patient taking SSKI, at 24 hr after I-131 MIBG. Salivary glands show clearly, but not thyroid.

The tissue distribution studies in dogs showed that the concentrations in the submandibular glands (which do not concentrate iodide) were 0.502% kg dose/g ± 0.059 (mean ± s.e.m., n = six glands) while those in the parotid glands (which do concentrate iodide) were 0.475 ± 0.124 (n = six glands).

Thus it appears that the activity observed in the salivary glands is not due to the concentration of free iodide.

Seven patients showed no salivary gland visualization at 48 hr after tracer injection. Of these, four were receiving tricyclic antidepressant therapy. Three of these took imipramine hydrochloride, a tricyclic antidepressant known to inhibit the neuronal uptake of norepinephrine and guanethidine (*13*). Two patients were taking the drug at a dose of 75 mg/day at the time of I-131 MIBG injection, while the third had been taking 40 mg/day until 7 days before I-131 MIBG injection. In two of the patients I-131 MIBG scintigraphy was repeated at 3 and 3½ wk following withdrawal of imipramine hydrochloride, and this time clear salivary gland images were obtained (Fig. 2). There was in addition a fourth patient who had taken doxepin hydrochloride 600 mg/day up to the time of I-131 MIBG injection. This drug is a tricyclic antidepressant with action similar to imipramine hydrochloride; it had a similar effect on the salivary glands, reducing visualization to a bare minimum.

One patient had evidence for severe autonomic neuropathy. His plasma catecholamine concentrations were extremely unusual in that on several occasions they demonstrated very low recumbent norepinephrine (NE) associated with normal epinephrine (E): NE 39, 24, and 15 pg/ml; E 80, 86, 50 pg/ml. There was no significant increase in norepinephrine on standing. These values suggested a severe adrenergic autonomic neuropathy. Figure 3 shows the posterior head-chest image of this patient, in whom no radioactivity was seen in any salivary gland.

In the remaining three patients, the causes of nonvisualization of the salivary glands could not be identified. The salivary glands were seen faintly on the 24-hr images that were available in two of them.

Examination of the salivary gland intensity between 24-hr and 48-hr images was possible in 64 patients. The intensity appeared to decrease between 24 hr and 48 hr in 53% of the cases, with no change in the rest.

The final case was that of a 72-yr-old white woman with a Horner's syndrome on the right side. She had episodes of headache, palpitations, and hypertension. She gave a history of thyroidectomy for goiter at age 40, with inadvertent sympathectomy leading to a complete right-sided Horner's syndrome. She was referred for I-131 MIBG imaging because of a suspicion of pheochromocytoma. Anterior and lateral head images with I-131 MIBG were added to the routine images. After obtaining the informed consent, salivary gland imaging

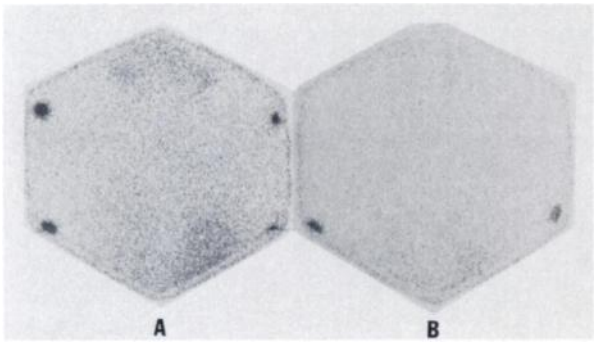

FIG. 2. (A) Salivary glands are seen on 48-hr posterior head-chest I-131 MIBG image, 3 wk after discontinuation of imipramine hydrochloride administration. (B) They had failed to show on 48-hr posterior head-chest I-131 MIBG image taken during administration of drug (75 mg/day).

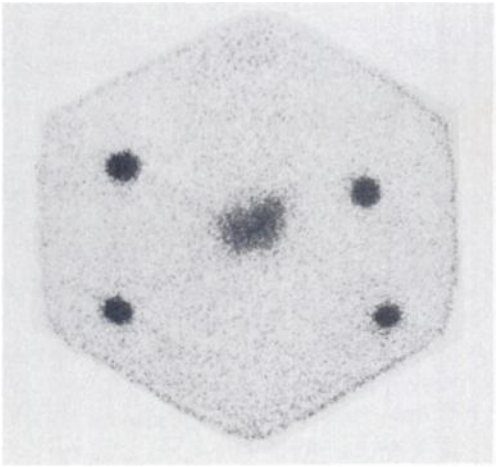

FIG. 3. Posterior head-chest image at 24 hr after I-131 MIBG, from patient with idiopathic autonomic neuropathy. No radioactivity appears in salivary glands; thyroid accumulation is due to inadvertent omission of iodide administration. Four radioactive surface markers are on shoulder tips and axillae.

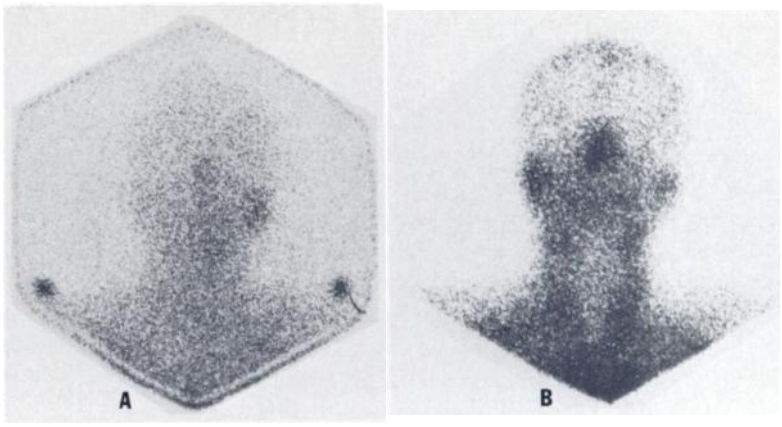

FIG. 4. Anterior images of patient with right-sided Horner's syndrome. Discrepancy in right salivary gland visualization is obvious between 24-hr I-131 MIBG (A) and 20-min $^{99m}TcO_4^-$ (B) images.

was performed 20 min after intravenous injection of 5 mCi of Na $^{99m}TcO_4$, and the two sides were compared. The concentration mechanism for pertechnetate in the salivary glands is similar to that of iodide (*14–16*), and thus this experiment permitted the examination of the uptake of I-131 MIBG in neuronal elements and Tc-99m by glandular acini.

Figure 4 contrasts the findings in the salivary glands between I-131 MIBG (A) and $^{99m}TcO_4^-$ (B) imaging in this patient with right-sided Horner's syndrome. The difference in the salivary gland images is striking in the two studies. The right-sided glands are not seen with MIBG, whereas they are a bit darker, if anything, with pertechnetate, especially the parotid.

Excretion mechanisms. Table 2 shows radioactivity from I-131 MIBG in plasma and saliva, and the saliva-to-plasma ratio with time. The mean radioactivity was highest at 15 min, then declined in both plasma and saliva. The saliva-to-plasma ratio was greater than 1.0 at all times. The greatest mean ratio was observed at 4 hr. Chemical forms of the radioactivity were 98% free I-131 and 2% I-131 MIBG in the unstimulated saliva, and 93% and 7%, respectively, in the saliva stimulated with chewing gum. The activity excreted in the saliva represented only a minute fraction of that in the salivary gland.

DISCUSSION

The data summarized in Table 1 show that the mechanism of salivary gland uptake of I-131 MIBG is not simple concentration of radioiodide. Although the dosage of iodide (40–130 mg/day) was sufficient to block iodide uptake by the thyroid, such doses may not fully inhibit uptake by the salivary glands and stomach (*16–19*). However, only the salivary glands were visualized, and never the stomach despite the fact that both organs can concentrate I-131 ions (or $^{99m}TcO_4^-$) by the same mechanism and with similar affinity (*9,20*). This discrepancy between salivary gland and gastric visualization precludes a simple concentration of I-131 ion, and suggests a specific uptake of I-131 MIBG. The tissue studies in dogs likewise show that I-131 MIBG is equally concentrated in the submandibular and parotid glands, both being sympathetically innervated (*10,11*), although only the parotid is able to concentrate iodide.

The neuronal nature of the I-131 MIBG uptake is further suggested by:

1. The inhibition of such uptake by tricyclic antidepressants. I-131 MIBG is a derivative of guanethidine, and shows structural similarities to norepinephrine (*1,2*). High concentrations of radioactivity from C-14 guanethidine have been found in the salivary glands of mice on whole-body autoradiography (*21*). Antagonism of guanethidine by tricyclic antidepressants has been well documented (*22–24*). It inhibits the norepinephrine uptake mechanism in the peripheral adrenergic neuron in man and thereby prevents uptake of guanethidine at its site of action (*13*).
2. The lack of I-131 MIBG uptake by the salivary

TABLE 2. RADIOACTIVITY (10^{-5} × cpm/l, mean ± s.e.m.) FROM I-131 MIBG IN PLASMA AND SALIVA, AND SALIVA-TO-PLASMA RATIO

	Time after I-131 MIBG injection				
	15 min	1 hr	4 hr	24 hr	48 hr
Plasma	11.9 ± 1.3(9)*	6.5 ± 0.8(9)	4.4 ± 0.6(9)	2.5 ± 0.5(7)	1.8 ± 0.3(8)
Saliva	72.4 ± 10.5(9)	55.2 ± 7.0(9)	53.3 ± 8.2(9)	20.8 ± 2.7(9)	10.8 ± 2.9(8)
Saliva/Plasma ratio	6.9 ± 1.3(9)	9.6 ± 1.6(9)	13.1 ± 2.1(9)	10.8 ± 2.7(7)	5.9 ± 1.6(8)

* ( ) = No. of patients.

glands of a patient suffering from severe autonomic neuropathy.

3. The ipsilateral decrease in I-131 MIBG uptake by the salivary glands of a patient with specific adrenergic sympathetic denervation of these glands due to surgically induced Horner's syndrome.

Although the secretion of saliva is primarily governed by parasympathetic innervation of the salivary glands, these organs receive a rich sympathetic innervation and are sites of norepinephrine uptake (*25*). The sympathetic nervous system serves to modulate the composition of saliva secreted (*26*). The clearance of I-131 MIBG from the plasma was very rapid and the saliva-to-plasma ratio of radioactivity was always greater than 1.0 from 15 min to 48 hr after I-131 MIBG injection. The majority of radioactivity in the saliva was in the form of free I-131 ion. Stimulation by chewing caused a slight increase in I-131 MIBG in the saliva. This excretion of radioactivity represents only a small fraction of that in the gland.

The source of both the free I-131 and I-131 MIBG is probably the sympathetic neurons of the salivary glands, although some direct concentration of the radiopharmaceutical by acinar cells may occur. However, the I-131 MIBG seen in images of the salivary glands appears to be principally the neuronal component.

Salivary gland imaging with radioiodinated MIBG may be useful in assessing disorders of the gland's sympathetic innervation, and thus may be a "diagnostic mirror" of a generalized adrenergic neuropathy such as that of diabetes.

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