Indium-111-DTPA-Octreotide Uptake Measured in Normal and Abnormal Pituitary Glands

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Pituitary uptake of [^{111}In-DTPA]-octreotide is highly variable, and no formal methods for quantification have been described. Conflicting results have therefore been published as to the presence of somatostatin receptors in nonsecreting adenoma of the pituitary gland. The aim of the present study was to define the most accurate method for the analysis of [^{111}In-DTPA]-octreotide SPECT studies of the pituitary gland. **Methods:** We used a multidetector brain SPECT camera to measure pituitary uptake of [^{111}In-DTPA]-octreotide in healthy volunteers and patients with and without pituitary adenoma. For quantification, two methods were compared, one involving a manually drawn ROI and one a fixed ROI, as to their reliability and discriminative power. The optimal time interval after injection was also studied in the volunteers. **Results:** Optimal images were obtained 24 hr after injection. Correction for background activity is not useful in view of the very low counts at that time which result in highly fluctuating ratios. Lower variability was observed in the fixed ROI method in which activity was expressed as counts corrected for dosage and body weight. **Conclusion:** A fixed ROI method without background correction is the most reliable way to measure pituitary uptake of [^{111}In-DTPA]-octreotide. This method allows for good separation of somatostatin-receptor-positive adenomas from normal pituitary glands.

Key Words: indium-111-DTPA-octreotide; pituitary glands; SPECT

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Visualization of somatostatin (SMS) receptors in vivo has become increasingly important for the diagnosis, prediction of therapeutic effect of octreotide and follow-up treatment in endocrinological tumors (*1*). This may also be applicable to pituitary adenomas. The normal pituitary gland has SMS receptors, and pituitary tumors may contain these as well. The SMS receptor density as measured in vitro is highest in growth hormone (GH) secreting adenomas. Prolactinomas may contain SMS receptors as well (although a factor of 4 lower), whereas no or only very low quantities have been reported in nonsecreting pituitary adenomas (*2*). Other studies have shown that SMS receptors can be present in nonsecreting adenomas in vitro (*3*).

Several studies have been conducted on the uptake of labeled octreotide in pituitary adenomas (*4–6*). In these studies, no formal control group was used and the uptake into the pituitary gland was not quantified but assessed as being positive or negative on planar or SPECT images. No attempts for more precise quantification were made, which, in view of the reported variability of the visualization of the hypophysis (*7*), is important. The conflicting results in nonsecreting adenomas may be caused by differences in subjective judgement of the images.

To address this problem, we conducted a study of normal volunteers, patients without pituitary adenoma and some patients with pituitary adenoma to develop a quantitative method to measure normal and abnormal pituitary uptake of [^{111}In-DTPA]-octreotide.

We used a brain-dedicated multidetector SPECT camera with high sensitivity to optimize imaging of the pituitary gland both in health and disease. We tried to find the optimal time after injection of the radiopharmaceutical for imaging. We further examined which semiquantitative approach would be most discriminative between SMS-receptor-containing macroadenomas and normal pituitaries.

MATERIALS AND METHODS

Subjects

Eighteen patients and six healthy volunteers were examined. All subjects gave informed consent to participate in the study. Age, sex and diagnosis are given in Table 1.

SPECT Imaging

SPECT imaging was performed after injection of 29-242 MBq [^{111}In-DTPA]-octreotide. The administered dose ranged from 29 to 66 MBq in the healthy volunteers, and from 87 to 242 MBq in the patients. A lower dose was used in the volunteer study to comply with the regulations of the hospital's Medical Ethics Committee.

For imaging, a high-sensitivity, high-resolution multidetector neuroSPECT system fitted with 12 high-resolution 800 hole collimators was used. This system has an inslice resolution of 6 mm (FWHM of a line source in air), a slice thickness of 1.2 cm and a sensitivity of 315–520 kcts/sec per MBq/ml/slice for ^{99m}Tc (*8*).

In the volunteer group, dynamic SPECT imaging was started immediately after injection for 30 min, each slice lasting 150 sec, followed by multiple multislice studies, starting from the cantomeatal line at various time points up to 48 hr after injection. In the latter part of the study, the imaging time was 5 min/slice with an axial spacing of 10 mm. Energy windows were set at 147–187 and 221–271 keV. Images were reconstructed in the middle resolution mode with one iteration and with a gain factor of 16 using a dedicated software program. Uniform attenuation equal to that of water was assumed in an ellipse drawn optimally around the brain.

In the patient group, a multislice study was made 24 hr postinjection only.

Quantification Methods

We used two methods to determine SMS receptor binding potential in the pituitary gland.

Method 1. A manual region of interest (ROI) of the pituitary was drawn by two independent observers for the three optimal slices in which the pituitary was visible employing a lower threshold of 50% isocontour.

Method 2. A fixed ROI of the pituitary gland was used to standardize its size, so that the only variable was the concentration of SMS receptors on the pituitary. The following sizes for the mean pituitary were obtained: length 0.75 cm; width 1.00 cm; height 1.50 cm (*9*). Thus, a fixed ROI of 0.75 × 1.00 cm was made and placed over the three optimal slices in which the pituitary was visible. The

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TABLE 1
Data on Volunteers and Patients without Pituitary Adenoma

Subject no.	Age (yr)	Sex	Activity*	Diagnosis
1	23	Male	494	Normal volunteer
2	24	Male	270	Normal volunteer
3	45	Male	226	Normal volunteer
4	52	Female	191	Normal volunteer
5	52	Female	192	Normal volunteer
6	28	Male	333	Normal volunteer
7	53	Male	94	Medullary thyroid cancer
8	54	Female	370	Graves' disease
9	67	Female	327	Carcinoid
10	67	Female	169	Carcinoid
11	28	Female	255	Carcinoid
12	25	Female	198	Pheochromocytoma
13	36	Male	231	Carcinoid
14	22	Male	396	Medullary thyroid cancer
15	30	Female	274	Carcinoid
16	35	Female	342	Carcinoid
17	50	Male	360	Crohn's disease
18	40	Male	323	Chronic pancreatitis
19	40	Female	181	Graves' disease
20	24	Female	209	Graves' disease

*Pituitary activity is given in arbitrary units as defined by Method 2, measured 24 hr postinjection.

mean was then divided by the injected dose and multiplied by 100. The result was then corrected for radioactive decay and multiplied by the weight of the subject in kilograms. The slice with the highest value was chosen as the optimal one and used for further interpretation and comparison.

For both methods, the activity within the ROI was calculated in units called SMUs (Strichman Medical Units), which are proportional to radioactivity per unit volume. The approximate conversion to known activity is: 1 SMU = 100 Bq/ml. A background area

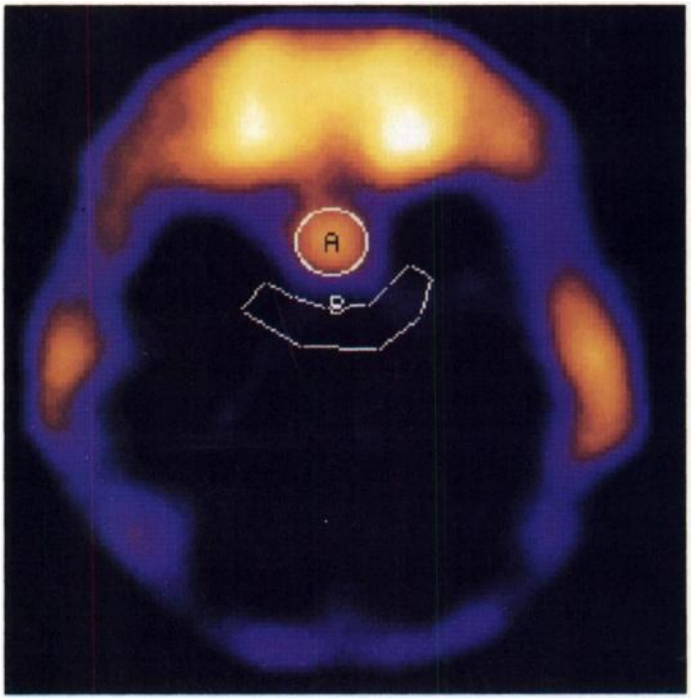

FIGURE 1. SPECT study of the pituitary gland in a 23-yr-old man (volunteer) 24 hr after i.v. injection of 56 MBq of [^{111}In-DTPA-D-Phe]-octreotide. Standardized ROI according to Method 2 was placed over the pituitary gland area as well as the background area.

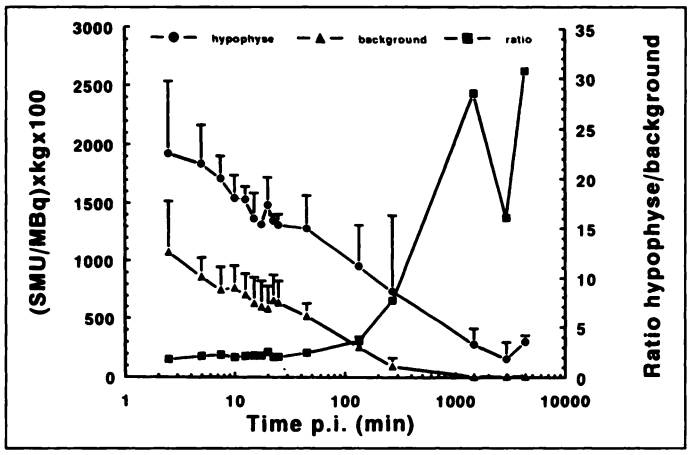

FIGURE 2. Time curve of radioactivity in the pituitaries of 6 healthy volunteers after i.v. injection of 29–66 MBq [^{111}In-DTPA-D-Phe]-octreotide.

was defined within the contours of the skull posterior to the pituitary gland as depicted in Figure 1.

Statistical Analysis

The ROI total activity, area and mean activity concentration in 49 slices in 15 patients as determined by 2 independent observers were compared using Wilcoxon's signed rank sum test and Spearman's rank correlation coefficient to decide the statistical significances of the differences and of the level of association, respectively (*10*).

An estimate of the variability of the results of the two observers was obtained by dividing the absolute difference by the mean of both observers and multiplying this by 100%:

$$\text{Relative \% Difference} = \frac{\text{Absolute[Observer A} - \text{Observer B]}}{((\text{Observer A} + \text{Observer B})/2) \times 100\%}.$$

In this way, the mean as well as the maximal possible absolute difference (either in a positive or in a negative direction) could be estimated as a percentage of the obtained value.

The healthy volunteers, patients with a pituitary adenoma and patients without pituitary adenoma were compared using the Mann-Whitney U-test (*10*).

RESULTS

Dynamic Studies

After the injection of [^{111}In-DTPA]-octreotide, radioactivity accumulated rapidly in the pituitary area of the volunteers, with maximal uptake occurring within the first 10 min. After that, the activity decreased with a biological $t_{1/2}$ of 72 min (Fig. 2). The background activity of the interior of the skull dropped to almost zero 300 min after injection, resulting in a sharp increase of pituitary-to-background ratio. In view of the very low counts after that time, it was concluded that background correction was not useful.

Quantification Methods

The variability of both quantification methods was studied using the 24-hr images of volunteers and patients. The first method, using manually drawn ROIs, proved to be inappropriate, since it resulted in a large interobserver variability (Table 3). The mean relative percentage difference was highest for the ROI area (38%), indicating a substantial difference in the size of the ROI drawn. This difference proved to be systematic as the Wilcoxon's signed rank sum test was significant, showing a bias between the two observers. Most disagreements occurred within 136% for the area, within 117% for the activity and within 36% for the mean estimated concentration of radioactivity in the ROI.

TABLE 2
Data for Patients with Pituitary Adenoma

Patient no.	Age (yr)	Sex	Activity*	Diagnosis
1	28	Male	593	TSH/PRL producing adenoma
2	36	Female	713	TSH producing adenoma
3	73	Male	524	Malignant prolactinoma
4	49	Male	888	Nonsecretory adenoma
5	42	Female	268	Nonsecretory adenoma
6	44	Female	870	Nelson's syndrome

*Pituitary activity is given in arbitrary units as defined by Method 2 measured 24 hr postinjection.

The second method proved to be superior, since the mean estimated radioactivity concentration within the fixed ROI showed no significant difference between the two observers.

Static Studies

Fixed ROIs (Method 2) were used to compare the volunteer and patient groups as to pituitary activity 24 hr postinjection. Individual values are given in Table 1. The average activity was 284 ± 116 in the normal volunteers and 276 ± 94 in the patient group without pituitary involvement. No significant difference was observed between the values in the volunteers and the "normal" patient group (Mann-Whitney U-test), therefore these results were combined, resulting in a normal value of 272 ± 96. For patients with pituitary adenoma, only one patient (no. 5) had a value (268) below the upper level of the normal, 464 (normal average + 2 s.d.). This patient suffered from a nonsecretory pituitary adenoma. The values observed in the other patients are given in Table 2. Figure 3 demonstrates the scatter of the values in the three groups.

DISCUSSION

We observed that the accumulation of [^{111}-DTPA]-octreotide in the pituitary is indeed highly variable. In a normal population, we found that the level may vary about fivefold in the absence of pituitary disease. This finding stresses the importance of standardization in the study of adenoma. The conflicting results in earlier studies may therefore be explained by insufficient methodology.

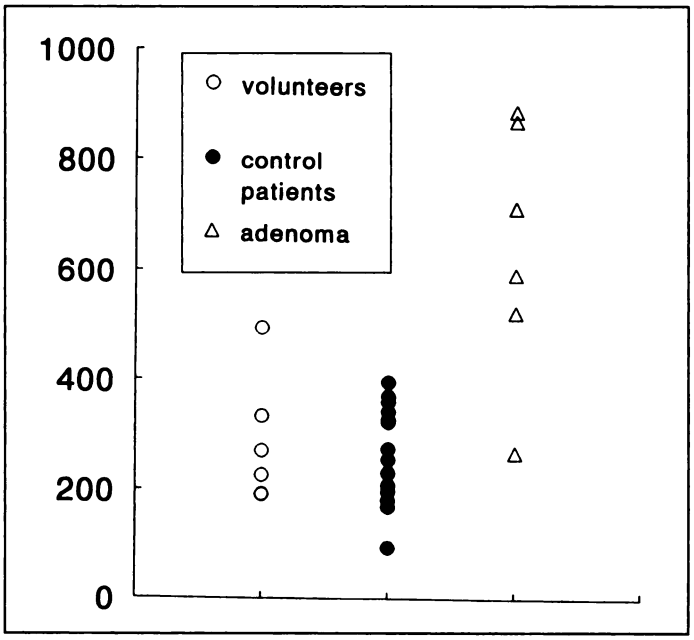

FIGURE 3. Scatter of pituitary activity values as determined by Method 2 in the three groups studied 24 hr after injection of [^{111}In-DTPA-D-Phe]-octreotide.

TABLE 3
Interobserver Variability of Both Methods

	Method 1		Method 2	
	Activity	Area	Activity	Area
Rel. %Difference	33	38	5	3
s.d.	42	49	2	2
Wilcoxon test (p value)	0.0016	0.0003	ns	ns

A fixed ROI placed on the slice with the maximal proved to be superior to manually drawn ROIs for estimating the pituitary octreotide receptor binding potential, especially if a large variability was observed in the surface of the area drawn by the observers. This could be decreased considerably by placing a fixed ROI on the pituitary gland area. A better approach would probably be the matching of CT or MR images with the SPECT result and drawing the ROI on the former anatomical study. This approach would be especially helpful in the case of an enlarged sella. The best images were obtained 24 hr postinjection, since the pituitary was optimally visualized compared to the background. This finding agrees with that in previous reports (*1,7*).

The octreotide receptor binding potential in the patients group with pituitary adenoma was significantly higher than in the healthy volunteers or in the patients without pituitary disorder. Therefore, quantitative [^{111}In-DTPA]-octreotide SPECT may be helpful in the diagnosis of pituitary adenomas and the monitoring and follow-up of octreotide treatment. This method may help determine whether nonsecreting adenomas mostly contain high levels of SMS receptors.

This method also enables the study of the factors influencing the observed large variation in octreotide binding to the pituitary gland. Such factors may include sex, age, circadian activity and hypothalamic activity.

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