Iodine-123-Tyr-3-Octreotide Uptake in Pancreatic Endocrine Tumors and in Carcinoids in Relation to Hormonal Inhibition by Octreotide

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Uptake of ^{123}I-Tyr-3-octreotide (TOCT) by hormone-secreting abdominal tumors was studied to compare scintigraphic observations with the reduction in hormone levels brought about by a brief therapeutic test. **Methods:** A prospective study was conducted on 17 patients, totalizing 46 proven lesions, with endocrine tumors of the pancreas (10 patients, 20 lesions) and/or carcinoid metastases (8 patients, 26 lesions). Tumor hormonal hypersecretion was inhibited by octreotide. **Results:** There was good agreement between the results of these examinations. **Conclusions:** The detection of abdominal tumors using this radiotracer is strongly related to its functional characteristics. Variations in the scintigraphic and test results according to different tumor types were in agreement with published data on the density of somatostatin receptors measured by in vitro studies or scintigraphy and by the therapeutic effects of octreotide.

Key Words: octreotide; ^{123}I-Tyr-3; carcinoid tumor; endocrine tumor

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The presence of somatostatin receptors (*1*) in a wide variety of tumors has been demonstrated in vitro by biochemical studies and autoradiography (*2,3*) and in vivo by scintigraphic visualization after intravenous administration of radiolabeled somatostatin analogs, first using ^{123}I-Tyr-3-octreotide (*4–6*) (TOCT), and more recently with ^{111}In-pentetreotide (*7–9*). The tumors reputed to have the highest densities of somatostatin receptors are those of a neuro-endocrine character (pituitary adenomas, endocrine tumors of the pancreas, carcinoids, pheochromocytomas, thyroid medullary cancers, small-cell adenocarcinomas, etc.), certain cerebral tumors (astrocytomas, meningiomas), mammary adenocarcinomas and lymphomas (*10*). In pancreatic endocrine tumors, scintigraphic in vitro and in vivo studies have given similar results (*11*) that tend to show that scintigraphic visualization of tumors was related to the abundance of somatostatin receptors (*11,12*).

Treatment by delayed-action somatostatin analogs, such as octreotide (*13,14*), can be of benefit to patients with endocrine tumors of the digestive tract (*15*). In this case, a decrease in the levels of hypersecreted hormones is recorded and associated with clinical improvement. Therapeutic effectiveness is determined by an abundance of somatostatin receptors in these tumors, which is generally correlated with the ability to scintigraphically visualize the tumors using radiolabeled analogs of somatostatin (*16*).

The aim of this work was to study TOCT uptake by hormone-secreting abdominal tumors (endocrine tumors of the pancreas and carcinoids) and to compare scintigraphic observations with the reduction in hormone levels brought about by a brief therapeutic test using octreotide.

MATERIALS AND METHODS

Patients

This prospective study was approved by the local ethical committee (Comité de Protection des Personnes dans la Recherche Biomédicale du CHU de Lille). It involved 17 patients (9 females, 8 males, age 30–80 yr; mean: 50 yr) with 46 tumoral localizations characterized by hormonal hypersecretion and documented by radiological examinations (sonography, radiography, CT and/or MRI). Clinically, the patients showed few symptoms: infrequent flushing or flushing set off by meals or alcoholic drinks (6 patients) and/or moderate diarrhea (5 patients) in the case of carcinoids or abdominal pain (3 patients) and sometimes a history of ulcers (2 patients) in the cases of gastrinomas, or of necrolytic migratory erythema in one case of glucagonoma. Thirteen of the 17 patients had surgery. Thus, complete macroscopic, anatomical, histological and immunohistological data were available.

In 10 patients, the tumors were primary endocrine tumors of the pancreas or secondary tumors mainly of hepatic sites (Table 1): gastrinomas located in the pancreas or duodenum (5 patients), glucagonomas (3 patients) or insulinomas (2 patients). In eight patients they were metastases of carcinoid tumors located in the

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TABLE 1
Characteristics of Endocrine Tumors and Results of the Octreotide Test and ^{123}I-Tyr-3-Octreotide Scintigraphy

Patient no.	Type	Tumor	Site	Size	Evol	M	Test	TOCT
1	Glucagonoma*	+	Pancreas	30	0	−	2,1 +	+
2	Glucagonoma	+	Liver	20	1 yr	+	1,9 +	+
3	Glucagonoma*	−	Pancreas	−	0	−	1,0 −	−
4	Insulinoma	−	Liver	−	8 yr	−	1,0 −	−
5	Insulinoma	+	Pancreas	20	2 yr	−	1,6 +	−
6	Gastrinoma	+	Pancreas	50	2 yr	−	7,9 +	+
7	Gastrinoma	+	Duodenum	30	3 yr	+	10,0 +	+
8	Gastrinoma	+	Liver	50	11 yr	+	1,2 −	−
9	Gastrinoma	+	Pancreas, liver	20	1 yr	++	3,8 +	±
10	Gastrinoma†	+	Liver, skeleton	20	4 yr	+	1,8 +	+
10	Carcinoid†	+	Liver	20	6 mo	+	1,0 −	+
11	Carcinoid	+	Liver	30	6 mo	+	1,7 +	+
12	Carcinoid	+	Liver	60	3 mo	+	2,6 +	+
13	Carcinoid	+	Liver	15	1 mo	++	1,0 −	−
14	Carcinoid	+	Liver	10	1 mo	++	1,0 −	−
15	Carcinoid	+	Liver	50	6 mo	+	2,0 +	+
16	Carcinoid	+	Lymph node	20	2 mo	+	2,8 +	+
17	Carcinoid	−	Peritoneum	−	1 mo	+	1,1 −	±

*Patient explored because of multiple endocrine neoplasia.
†Patient with two types of tumor.
Size (mm) of smallest surgically proven endocrine tumors; Evol: duration of evolution: years (yr) or months (mo); M: arguments of malignancy (+ if arguments, ++ if miliary); Test: ratio of hormonal basal value-to-value after 3 days of treatment by octreotide (+ if upon threshold 1.5); TOCT: ^{123}I-Tyr-3-octreotide scan (+ if positive, − if negative, ± if doubtful).

liver (6 patients), the mesenteric lymph nodes (1 patient), or peritoneum (1 patient). One of the patients (no. 10) had symptoms that were indicative of both a carcinoid (diarrhea, flushing, intermittently high levels of platelet 5-hydroxytryptamine over the last 6 mo) and a gastrinoma (abdominal pain but without gastroduodenal ulceration and hypergastrinemia, which lasted 4 yr).

Lesion size (recorded by the surgeon or estimated from radiological data) varied from 10 to 170 mm. In two patients (nos. 1 and 3), examinations were carried out during tests for recently discovered type II multiple endocrine neoplasia. In the other patients with endocrine tumors of the pancreas, the known period of development of clinical or laboratory, endocrine or cancerous symptoms was 4 yr on average (1–11 yr). Carcinoid metastases were studied in patients in whom the primary tumor had been surgically removed 1 mo to 10 yr previously and showed biological or clinical signs of evolutive regrowth since 3 mo on average (1–6 mo).

The malignancy of the tumors was defined by the rapidity of clinical changes and by histological signs of local or regional invasion and by the presence of metastases. Malignancy was considered as unestablished (−) when none of the above was present, as high (++) in the case of hepatic miliary (3 patients) and as moderate (+) in other cases when one of the above malignancy indicators was present.

Short-Term Dynamic Hormonal Test Using Octreotide

The levels of hormones secreted in excessively high quantities were measured immediately before and after a short treatment with octreotide (Sandostatine®, Sandoz, Basel, Switzerland): 100 μg subcutaneously twice a day for 3 days. Depending on the type of tumor, the comparison involved measuring either levels of gastrinemia (5 patients), glucagonemia (3 patients), insulinemia (2 patients) or of platelet 5-hydroxytryptamine (serotonin) and its urinary metabolite 5-hydroxyindoleacetic acid (5-HIAA) 24 hr later (8 patients). Plasma gastrin, glucagon and insulin were determined by specific RIAs using commercial kits supplied by CIS Bioindustrie (Gif/Yvette, France), Biodata (Rome, Italy) and Pasteur (Marnes la Coquette, France). Levels of serotonin bound to platelets were determined by fluorescent OPT assay (*17*), and urinary 5-HIAA was determined by a high-pressure liquid chromatography method (*18*).

The interpretation of the test was based on the ratio of the hormone levels before and immediately after the brief treatment. The test was judged negative (−) if this ratio was lower than 1.5 and positive (+) if above 1.5. This test was performed within 2 days to 2 wk before scintigraphy.

Scintigraphy with ^{123}I-TOCT

Radiochemical Preparation. TOCT was supplied by Sandoz (Basel, Switzerland). Iodine-123 (p, 5n) was provided by Mallinckrodt Medical (Petten, The Netherlands) in the form of sodium iodide to a high concentration (370 MBq in 40 μl) with a pH of 10 to 12. Iodine-123 labeling was carried out immediately before scintigraphy using the chloramine-T method described by Bakker (*4*). The injected solution was composed of 8 μg of ^{123}I-TOCT labeled with 250 MBq of ^{123}I in 2 ml of pH 4 acetate buffer, sterilized by filtration through a 0.22-μm Millipore® filter.

Patient Preparation. The patients were orally given Lugol's solution (solution of iodine in 5% potassium iodide) 1 drop/day/kg body weight and 1 g of potassium perchlorate 1 hr before tracer injection. A second drop was given the following morning. Tracer elimination via the biliary-fecal route was accelerated by eating a fatty meal and taking three liters of laxative (Fortrans®, Beaufour, France) the evening before injection.

Data Acquisition and Analysis. DSX and DS7 gamma cameras (Sopha Medical, Buc, France), equipped with a low-energy, high-

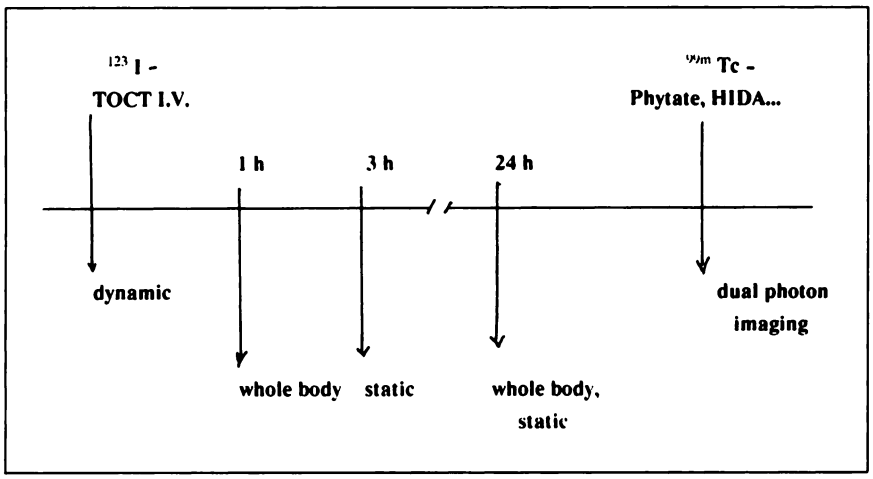

FIGURE 1. Time line diagram illustrates the imaging protocol.

resolution collimator (HRBE 8.140) or medium-energy, high-resolution collimator (HRME 11.250) were used. The spectrometry was adjusted to the emission peak for ^{123}I (145–173 keV). Patients were positioned in dorsal *decubitus*.

The DS7 camera was centered on the anterior abdominal area above the liver to detect probable secondary sites. Data acquisition was dynamic: sixty 1-sec images, then sixty 3-sec images and sixty 30-sec images with 64 × 64 × 8 matrices.

At 1 hr, 24 hr and occasionally at 48 hr, a body scan was obtained with the DSX at a speed of 15 cm/min, with anterior and posterior views. At 3 hr, centered images were obtained with the DS7 in 600 sec by static acquisition on a 512 × 512 × 256 matrix.

The scans were interpreted by two physicians unaware of the clinical history of the patient. In normal subjects, the activity of the heart and the major blood vessels appears rapidly on the trunk, followed by diffuse homogeneous uptake by the liver and uptake within the spleen that is usually less intense. After 3 min, low intensity renal activity appeared and then a vesical activity; after 5 min, biliary activity concentrates in the intra-hepatic bile ducts and then in the extra-hepatic ducts before being discharged into the intestine where its progress can be clearly followed after 4 hr and is still sometimes visible at 24 hr, despite the administration of a laxative. At 24 hr, the intensity of hepatic activity is clearly decreased, and at 48 hr the ^{123}I activity is generally too low for imaging.

The intensity of uptake assessed as being suspect by its location, early appearance on the dynamic images (before the third minute) and its persistence for 24 hr was compared with the physiological hepatic activity. Irrespective of location, uptake was assessed as normal (−) when distribution was as described above, doubtful (±) when extra-hepatic uptake was poorly defined and was of lower or equal intensity than activity in healthy liver or when hepatic activity was out of proportion with the image of functioning hepatic parenchyma tracer (phytate) without being abnormally high, and was positive (+) when uptake was well defined and had a greater intensity than that of healthy liver.

Additional Scans. If needed to identify healthy tissues and organs, technetium-labeled tracers were administered intravenously after the 24-hr TOCT scans; ^{99m}Tc-phytate for liver identification (37 MBq of ^{99m}Tc) and ^{99m}Tc-HIDA for hepato-biliary identification (37 MBq of ^{99m}Tc). The two spectral windows were therefore centered on the emission peaks of ^{123}I (151–167 keV) and ^{99m}Tc (133–151 keV), respectively. The schedule of the imaging protocol is given in Figure 1.

In one patient, bone scintigraphy was performed at a different time from the other imaging procedures by a whole-body scanner with the DSX equipped with an HRBE collimator and adjusted to the emission peak of ^{99m}Tc (128–156 keV) 3 hr after intravenous injection of 444 MBq of technetium-labeled phosphonates. In the same patient, MIBG scintigraphy was performed at 24 and 72 hr after injection of 37 MBq of ^{131}I-MIBG. Planar images were acquired with a DS7 camera equipped with a high-energy, high-resolution 15-360 collimator with the spectrometer adjusted to the emission peak of ^{131}I (325–395 keV).

Statistical Analysis

Because of the small size of our population and because it contained sub-groups, no statistical analysis was performed.

RESULTS

The tests and imaging sessions were clinically well tolerated. No side effects were noticed. In cases of glucagonoma or insulinoma, no disturbance of glycemia levels was recorded.

Scintigraphy with TOCT and test results are given in Table 1. Table 1 also shows whether tumoral lesions presumed to be rich in somatostatin receptors were anatomically proven to be present at radiologically suspect sites. Analysis of these results on a lesion-by-lesion basis is given in Table 2.

True-Positives. In nine patients (nos. 1, 2, 6, 7, 10, 11, 12, 15 and 16), early and prolonged increased uptake by 34 lesions interpreted as being clearly abnormal was confirmed by surgical and anatomical/pathological data. These tests were positive. The smallest tumor identified was 20 mm for abdominal tumors. A systematic whole-body search showed the presence of extra-abdominal metastases in one patient (no. 10). In this patient, a bone scan obtained 24 hr later demonstrated slight increased uptake of the osteotropic tracer at suspect sites. MRI later confirmed tumor location within the bone marrow. The octreotide test for this patient was positive for gastrin but negative for serotonin. MIBG scintigraphy only showed foci of hepatic

TABLE 2
Lesion-by-Lesion Analysis of ^{123}I-Tyr-3-Octreotide Scan Results Relative to Localization, Size and Type of Anatomically Proven Endocrine Tumors

Organ	Size (mm)	TOCT + or ±	TOCT −
Pancreas (duodenum)	<20	Gastrinoma (1)	Insulinoma (1)
	>20	Glucagonoma (2)	
		Gastrinoma (2)	
Liver	Miliary	Gastrinoma (1)	Carcinoid (2)
	<20	Gastrinoma, carcinoid* (4)	Glucagonoma (2)
		Carcinoid (1)	Carcinoid (2)
	>20	Glucagonoma (2)	Gastrinoma (1)
		Gastrinoma, carcinoid* (4)	Gastrinoma, carcinoid (1)
		Carcinoid (11)	Carcinoid (3)
Lymph node	<20	Carcinoid (1)	
Skeleton	<20	Gastrinoma, carcinoid* (5)	

*Patient with two types of tumor.
TOCT: ^{123}I-Tyr-3-octreotide scan (+ if positive, − if negative, ± if doubtful).

increased uptake, whose location differed from results obtained with TOCT. Anatomical examination of one of the hepatic tumors revealed that the tumor, which bound anti-serotonin antibodies, had a small contingent of other cells that were intensively bound to anti-gastrin antibodies.

True-Negatives. In two patients (nos. 3 and 4), an evolutive recurrence of glucagonoma or of insulinoma that had been previously surgically removed was suspected from the biological results and sonographic and CT images of the liver and pancreas. Nevertheless, no abnormal uptake was recorded. In these patients, testing was negative and arteriography was normal. Eighteen months later, these patients were asymptomatic and second surgery was not necessary.

Doubtful Scans. In one patient (no. 17), from whom a carcinoid of the small intestine had been surgically removed less than 1 mo previously, scintigraphy showed a slight diffuse abdominal increase of uptake which was interpreted as doubtful (±), whereas the test was negative. Anatomical investigation showed histological lesions of a secondary peritoneal carcinomatosis originating from hepatocarcinoma. In one patient (no. 9) with an anatomically malignant 20-mm gastrinoma in the tail of the pancreas and with secondary miliary in the liver, there was only a slight diffuse intensification of abdominal uptake below the umbilicus which was scintigraphically doubtful, but the test was strongly positive (ratio 3.8).

False-Negative with Scintigraphy Alone. In one patient (no. 5) with a 20-mm insulinoma of the head of the pancreas without signs of malignancy, no abnormal uptake was observed. The test was just positive (ratio 1.6). Excision of the tumor returned insulinemia to normal levels. In patients with hepatic metastases, eight lesions other than the main lesion were not seen; four lesions were less than 20 mm, and in other patients, four were carcinoid metastases.

False-Negative with the Test Alone. Only Patient 10 had a false-negative result with only one of the tests performed.

False-Negatives with the Test and Scintigraphy. In three cases, despite the presence of tumors reputedly rich in somatostatin receptors, TOCT scans and octreotide tests were both negative. In one of these patients in whom symptoms had persisted for 11 yr (no. 8), surgery revealed the existence of a 50-mm partly necrotic hepatic metastasis of a gastrinoma. The immunohistochemistry test was positive for chromogranin and was slightly positive for gastrin. In the two other cases (nos. 13 and 14), there was a miliary hepatic carcinoid.

DISCUSSION

According to several authors using various protocols (*15,19–23*), somatostatin analog therapeutic effectiveness, expressed as the percentage decrease from the initial value, varies depending on the type of tumor. We have drawn up our test on the basis of the therapeutic use of octreotide in a multicenter study concerning 78 patients with an endocrine tumor of the alimentary system (*15*); doses varied from 100 to 1200 μg/day and benign side effects were recorded. In our test we chose a daily dose of 200 μg, as this was effective but avoided harmful effects. A 3-day duration was chosen because a longer test could let potential regulation mechanisms to occur (*24*). The threshold value of 1.5 is equivalent to a 33% decrease in hormonal levels and therefore to a major change in hormonal secretion.

Octreotide test results and scintigraphic results were in good agreement in 17 of 15 patients; both modalities were positive in nine patients and both were negative in six patients. Patient 17 showed diffuse moderate abdominal uptake which was in disagreement with a negative test. This patient had peritoneal carcinomatosis from an hepatocarcinoma. Abnormal uptake of the somatostatin analog could have been due to a postoperative inflammatory phenomenon, since lymphocytes are rich in somatostatin receptors (*10,25*).

As for therapeutic effectiveness, uptake of somatostatin radioanalog should vary depending on tumor type. This could reflect the existence of subclasses of somatostatin receptors. Reubi (*26*) showed differences in affinity of their receptors for somatostatin-28 and for its analogs such as octreotide. More recently, Srkalovic (*27*) confirmed the existence of subpopulations of somatostatin receptors. One of our patients with a 20-mm insulinoma (no. 5) had a test that was positive, whereas his scan was negative. The sensitivity of insulinomas to treatment by octreotide is inconsistent (*15*). Gastrinomas are known to be particularly rich in somatostatin receptors from in vitro and in vivo diagnostic and therapeutic studies (*10,11,15*). These studies have shown a high incidence of tumors with a high density of receptors among gastrinomas but their small size sometimes makes them difficult to locate before and even during surgery. In one case with a necrotic gastrinoma metastasis (no. 8), both the negative octreotide test and TOCT scan could be explained by cell lysis and restricted access of analogs to cell receptors. In three patients with primary gastrinomas, the test was positive. Scintigraphy was positive in two patients where the tumors measured 50 mm and 30 mm in diameter (nos. 6 and 7), but doubtful for one tumor whose diameter was scarcely 20 mm (no. 9). In this patient, a highly malignant pancreatic gastrinoma was associated with miliary hepatic metastases. In two other patients, hepatic miliary-type metastases of a carcinoid were recently discovered (nos. 13 and 14) and the scan and the test both produced false-negative results. These last three patients were all remarkable for the rapidly developing nature of the tumor and for negative TOCT scans. Using animal or human cancer cell lines grafted onto nude mice, several authors have already correlated the inhibition of tumor growth by somatostatin due to the presence of somatostatin receptors within the tumor (*11,28–31*). Further analyses are, however, needed to determine to what extent uptake of indicators of neuro-endocrine differentiation such as somatostatin analogs are potential predictors for tumor development.

In one patient with two types of tumor (no. 10), we were tempted to attribute the intense and multiple hyperfixations of TOCT to metastases of the gastrinoma, which is known to have high densities of somatostatin receptors. On the other hand, increased uptake of ^{131}I-MIBG in some of the hepatic nodules could be attributed to carcinoid metastases. Anyway, radiolabeled analogs of somatostatin and ^{131}I-MIBG, which are taken up by tumors through two different mechanisms involving different cellular targets, should be considered as two separate and complementary markers of neuro-endocrine differentiation (*32*). By combining scans obtained with somatostatin analogs and those with MIBG, the possibilities of treating each lesion either with octreotide or with ^{131}I-MIBG can be assessed (*33*).

In comparison to the somatostatin analog radiolabeled with ^{111}In, TOCT has the disadvantage of being eliminated by the biliary-intestinal route. The use of the former tracer should provide improvement in the detection of abdominal tumors of less than 20 mm in diameter by decreasing artifacts, providing delayed images and improving scintigraphic contrast (*9,34*). Nevertheless, in the 17 patients we examined, the factors determining the uptake of radioanalogs of somatostatin were mainly functional factors as reflected in the hormonal inhibition test, rather than physical considerations concerning the tracer or the geometry of the tumor. The good agreement between the TOCT test and scintigraphic results suggests that the test could be used to assess the appropriateness of performing octreotide scintigraphy.

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