Indium-111 Activity Concentration in Tissue Samples After Intravenous Injection of Indium-111-DTPA-D-Phe-1-Octreotide

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Methods: Indium-111 activity concentrations in human tumor and normal tissue samples were determined at 24, 48 and 120 hr after i.v. injection of ^{111}In-DTPA-D-Phe-1-octreotide. Fourteen patients were included in the study. Seven patients had medullary thyroid carcinoma, four had midgut carcinoid tumors, two had endocrine pancreatic tumors and one had chronic pancreatitis. **Results:** For midgut carcinoids, the tumor-to-blood ratio was 51:220, for medullary thyroid carcinoma 4:39, and for two endocrine pancreatic tumors 6 and 1500. Tumor-to-muscle ratios varied between 1 and 1200 and tumor-to-fat between 2 and 1500 depending on tumor type. **Conclusion:** The sometimes extremely high tumor-to-normal tissue ratios present the possibility for use of radiolabeled octreotide for radiation therapy of somatostatin receptor positive tumors.

Key Words: octreotide; indium-111, neuroendocrine tumors; somatostatin receptors

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An increased number of somatostatin receptors has been found in neuroendocrine tumors (1,2). The somatostatin analogue octreotide has a longer biological halftime than the native hormone somatostatin and is therefore more suitable for in vivo applications. Radiolabeling of octreotide with ^{111}In has been performed using DTPA as a chelating agent (3). Recently, somatostatin receptor scintigraphy was used with promising results to localize primary and metastatic tumors expressing somatostatin receptors (4–9).

The pharmacokinetics and dosimetry of ^{111}In-DTPA-D-Phe-1-octreotide has been estimated from scintigraphic studies and examinations of blood, urine and faeces samples (10). Such studies are needed for dosimetric calculations for radiation protection purposes. However, to evaluate the possibility of using radiolabeled octreotide for tumor therapy, it is necessary to obtain detailed information on activity concentrations and absorbed doses in tumor tissue and normal tissue. Tissue samples must be collected and measured at different times after injection.

In a recent study, we evaluated the use of a detector to localize midgut carcinoids and endocrine pancreatic tumors during surgery following injection of ^{111}In-DTPA-D-Phe1-octreotide (5). In some patients and in one with chronic pancreatitis, we collected blood and normal and tumor tissue samples during surgery performed 24, 48 or 120 hr after injection of the radiopharmaceutical. The study's purpose was to determine ^{111}In activity concentration in human tissue samples at different time intervals after injection of ^{111}In-DTPA-D-Phe-1-octreotide.

MATERIAL AND METHODS

Radiopharmaceutical

DTPA-D-Phe-1-octreotide and ^{111}In-chloride were obtained from Mallinckrodt Medical B.V. (Petten, The Netherlands). The radiolabeling of DTPA-D-Phe-1-octreotide with ^{111}In was performed according to the instructions of the manufacturer. Chromatography of the radiopharmaceutical was performed using instant thin-layer chromatography with sodium citrate (0.1M, pH 5) as the mobile phase. The fraction of peptide-bound ^{111}In was more than 98%.

Patients

Fourteen patients (7 male and 7 female; mean age 52 yr, range 28–72 yr) were included in this study (Table 1). Thirteen of the patients had previously verified neuroendocrine tumors, seven patients had persistent hypercalcitonemia after previous surgeries for medullary thyroid carcinoma (MTC), four had midgut carcinoid tumors (MC) with regional lymph node and hepatic metastases, and two had endocrine pancreatic tumors (EPT). In Patient 14, a multihormonal neuroendocrine tumor was suspected due to elevated levels of gastrin, calcitonin, chromogranin A and human chorionic gonadotropin (HCG). In the latter patient, no tumor uptake of the radiopharmaceutical was found during scintigraphy and no tumor was found during surgery. The histopathological diagnosis in this case was chronic pancreatitis and liver cirrhosis.

The patients received 190–350 MBq ^{111}In-DTPA-D-Phe-1-octreotide (20 μg) intravenously. Prior to administration, the activity of the injected solution was measured with a well-type ionization chamber. All patients with MC were on daily octreotide treatment (100 μg × 2 s.c.). In Patient 1, octreotide treatment was discontinued on the day of radiopharmaceutical injection and re-

Time after injection (hr)	Patient no.	Sex	Age (yr)	Disease	Number of tumor samples	C_{tumor} (%IA/kg) mean (range)	T/B range	T/M range	T/F range
24	1	M	60	MC	6	28 (14–52)	80–170	na	7.0–320
24	2	M	60	MC	5	16 (3.6–31)	53–200	37–140	2.8–24
24	3	M	52	MTC	9	1.4 (0.29–2.7)	4.1–39	0.80–7.6	na
24	4	M	47	MTC	†				
48	5	F	45	MC	3	7.8 (3.7–16)	51–220	290–1200	340–1500
48	6	M	28	EPT	1	0.39	6.3	7.3	2.0
48	7	F	47	EPT	1	78	1500	270	220
48	8	F	35	MTC	6	1.5 (0.28–2.5)	3.8–33	1.2–11	na
48	9	M	34	MTC	1	1.1	33	8.9	17
120	10	F	67	MC	1	3.9	100	41	13
120	11	M	51	MTC	4	0.51 (0.46–0.54)	15–18	3.8–4.4	14–17
120	12	F	61	MTC	†				
120	13	F	69	MTC	2	(0.57–1.3)	11–24	3.8–8.4	6.6–15
120	14	F	72	Chronic pancreatitis	†				

*Expressed as percent of injected activity per kilogram tissue (%IA/kg).
†No tumors were collected or available; na = not available; MC = midgut carcinoid; MTC = medullary thyroid carcinoma; EPT = endocrine pancreatic tumor; T/B = tumor/blood; T/M = tumor/muscle; T/F = tumor/fat.

instituted after surgery. The study was approved by the local isotope and ethical committees and informed consent was given by the patients.

Tissue sampling

The patients underwent surgery one (n = 4), two (n = 5) or five (n = 5) days after injection of the radiopharmaceutical. Tumor, lymph nodes with or without metastatic growth, blood and other easily available normal tissue samples such as fat and muscle, and sometimes liver, bone marrow, ileum, lymph and thymus, were taken. The gallbladder was removed in two patients and bile was collected. All tissue and fluid samples were weighed and the activity content of ^{111}In was determined as described below. Thereafter, histological examination of the excised tissue was performed.

In vitro measurements

The ^{111}In activity in small tissue samples was measured in a gamma counter equipped with a 7.6 cm (diameter) × 7.6 cm NaI(Tl) well crystal (3 cm hole diameter, 6 cm depth) and a single-channel pulse-height analyzer. The activity in larger tissue samples was measured with a gamma camera equipped with a medium-energy, parallel-hole collimator. Calibration factors between the sensitivity of the ionization chamber and the gamma counter as well as of the ionization chamber and the gamma camera were determined. Corrections were also made for detector background and for radioactive decay.

The ^{111}In activity concentration, C_{tissue}, was expressed as the fraction of the injected activity, $A_{injected}$, per unit mass of the tissue:

$$C_{tissue} = \frac{A_{tissue}/m_{tissue}}{A_{injected}} \times 100, \quad [\%IA/g] \qquad \text{Eq. 1}$$

where A_{tissue} is the ^{111}In activity of the tissue sample and m_{tissue} its mass. Tissue (Ti) to blood (B) ratios were calculated:

$$Ti/B = \frac{A_{tissue}/m_{tissue}}{A_{blood}/m_{blood}} = \frac{C_{tissue}}{C_{blood}}. \qquad \text{Eq. 2}$$

Tumor-to-(normal tissue) ratios and ratios between different normal tissues were calculated correspondingly.

RESULTS

Indium-111 activity concentrations in blood, plasma, serum, muscle, fat and lymph nodes are shown in Table 2. In general, the radioactivity concentration in blood from the patients with tumor decreased with time after the injection of the radiopharmaceutical, though there were considerable variations in the blood samples collected at a certain time after injection. Patient 14, who did not have a malignancy, had the highest ^{111}In activity concentration in blood of the five patients studied at 120 hr after injection. The radioactivity concentration in plasma and serum were similar within the same patient, with plasma-to-blood and serum-to-blood ratios of 1.4 and 1.5 without any change with time. The muscle-to-blood ratios varied between 1.3 and 5.5, the fat-to-blood ratios were 0.55–8.4 and the (lymph node)-to-blood ratios were 0.90–16, irrespective of time after injection.

The ^{111}In activity concentrations in bile, bone marrow, gallbladder, ileum, liver, lymph and thymus are shown in Table 3. In the two patients who underwent cholecystectomy 48 hr after injection, the bile-to-blood ratios were 260 (Patient 5) and 86 (Patient 7) and the gallbladder-to-blood ratios were 28 and 23. The (bone marrow)-to-blood ratios in two other patients (4 and 8) who underwent sternotomy were 1.7 and 1.6. With Patient 12, we had the opportunity to collect and analyze lymph from the left thoracic duct and

TABLE 2

TABLE 2
Indium-111 Activity Concentration in Various Tissue Samples*

Time after injection (hr)	Patient no.	C_{blood} (%IA/kg)*	C_{plasma} (%IA/kg)	C_{serum} (%IA/kg)	C_{muscle} (%IA/kg)	C_{fat} (%IA/kg)	$C_{lymph node}$ (%IA/kg)
24	1	0.29	0.32	0.32	na	0.16–2.01[‡]	0.26–0.40[§]
24	2	0.16	0.25	0.25	0.22	1.3[§]	1.9
24	3	0.070	0.11	0.11	0.36	na	na
24	4	0.10	0.17	0.17	0.13	0.099–0.21[§]	0.50–0.90[¶]
48	5	0.072	0.10	0.12	0.013	0.011	na
48	6	0.062	0.10	0.14	0.054	0.20	na
48	7	0.053	0.080	0.081	0.29	0.35	0.68
48	8	0.075	0.12	0.14	0.23	na	na
48	9	0.080	0.12	na	0.16	0.072	0.69
120	10	0.037	0.046	0.048	0.094	0.31	na
120	11	0.030	0.043	0.052	0.12	0.032	na
120	12	0.063	0.093	0.093	0.12	0.12	na
120	13	0.053	0.081	0.078	0.15	0.087–0.15[‡]	na
120	14	0.16	0.20	0.23	na	0.65	2.5

*Given as percent of injected activity per kilogram (%IA/kg).
[†]n = 4.
[‡]n = 2.
[§]n = 5.
[¶]n = 3.
na = not available.

the lymph-to-blood ratio was 1.4 in two different samples. Normal liver biopsies were taken from Patients 6 and 7 (at 48 hr) and 14 (at 120 hr) and the liver-to-blood ratios were 48, 45 and 35.

Table 1 shows the ^{111}In activity concentration and tumor-to-blood (T/B), tumor-to-muscle (T/M) and tumor-to-fat (T/F) activity concentration ratios in the histopathologically verified tumor samples. The T/B activity concentration ratios for patients with MC were higher than those for patients with MTC. Three MC tumors, one primary tumor, one lymph node metastasis and one liver metastasis together with two leiomyomas from the pelvic region were removed from Patient 5. The T/B for these MC tumors were 51, 56 and 220, respectively, and 5 and 11 for the leiomyomas. There was no evident change of T/B with

time after injection for the same tumor type. Several tumors were removed from Patients 1, 2, 3 and 8. Figure 1 shows ^{111}In activity concentration versus tumor weight for tumors from the same patient (3). The concentration was not obviously dependent on the tumor size in any of these four patients.

DISCUSSION

This study was performed in order to determine ^{111}In activity concentration in tissue samples after injection of ^{111}In-DTPA-D-Phe-1-octreotide. Fourteen patients were included in the study. Tissue samples were collected during surgery at 1, 2 or 5 days after injection of the radiopharmaceutical.

TABLE 3
Indium-111 Activity Concentration in Bile, Bone Marrow, Gallbladder, Ileum, Liver, Lymph and Thymus Samples

Time after injection (hr)	C_{bile} (%IA/kg)	$C_{bone marrow}$ (%IA/kg)	$C_{gall bladder}$ (%IA/kg)	C_{ileum} (%IA/kg)	C_{liver} (%IA/kg)	C_{lymph} (%IA/kg)	C_{thymus} (%IA/kg)
24	na	0.17 [4]	na	na	na	na	0.21 [1] 0.30 [4]
48	19 [5] 4.6 [7]	0.12 [8]	2.0 [5] 1.2 [7]	0.47 [5]	3.0 [6] 2.4 [7]	na	0.54 [8]
120	na	na	na	na	5.6 [14]	0.086 [12]	na

*Given as % of injected activity per kg tissue (%IA/kg). The numbers in brackets indicate the patient number.
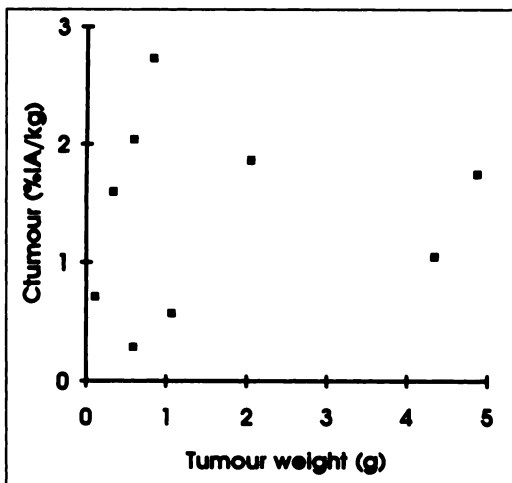na = not available.

FIGURE 1. Indium-111 activity concentration in tumor tissue vs. tumor weight. The tumor samples were collected from Patient 3 with medullary thyroid carcinoma at 24 hr after injection with ^{111}In-DTPA-Phe-1-octreotide.

At the same time-interval after injection there were large differences in radioactivity concentration in normal tissue between patients (Table 2). For blood, plasma and serum this difference corresponds to a factor of 4–5, but for muscle and fat tissue variations of up to a factor of 30–35 were noticed. In three patients, we observed large variations in the ^{111}In activity concentration in fat tissue samples taken from the same patient (Table 2, Patients 1, 4 and 13), possibly because the samples were collected from various locations and omenta. The highest concentration in blood at 120 hr after injection was found in the tumor-free patient with chronic pancreatitis and liver cirrhosis (Patient 14). The high radioactivity concentration in the blood of this patient could be due to absence of uptake in tumor tissue and low uptake by the cirrhotic liver. Low uptake in the liver has previously been observed in another patient with biopsy verified liver cirrhosis (Patient 21 (5)). Although ^{111}In activity concentration in tumor tissue was high in some of the patients, we did not observe lower radioactivity concentration in normal tissues in the patients with large total tumor burden. One cannot neglect the possibility that tumor burden itself could influence the pharmacokinetics of the radiopharmaceutical. For radiolabeled monoclonal antibodies, a faster clearance from blood and a decreased uptake in the liver has been observed in tumor-bearing rats compared with controls (11). Furthermore Trang et al. (12) have reported a correlation between total body clearance of radiolabeled monoclonal antibodies and relative tumor size in man.

The bone marrow-to-blood ratios obtained from two patients were 1.6. The bone marrow is one of the organs limiting therapy with radiopharmaceuticals. Estimations of the absorbed dose to the bone marrow are often based on the cumulated activity of the radionuclide in peripheral blood or biopsies containing red bone marrow, but also

cortical and trabecular bone for which corrections are made (13). The measured ^{111}In activity concentration in the two bone marrow samples (not containing any bone tissue) in this study suggests that there might be a risk of underestimating the absorbed dose to bone marrow if the estimations are based on measurements of peripheral blood.

There seems to be a difference in ^{111}In activity concentration between the different tumor types. The radioactivity concentration in tumor, T/B and tumor-to-(normal tissue) ratios were all higher for patients with MC tumors than for those with MTC, probably reflecting differences in distribution of somatostatin receptor types and receptor densities between the two tumor types (1,14,15). The T/B ratios found in the present study on neuroendocrine tumors after ^{111}In-DTPA-D-Phe1-octreotide injection by far exceed those reported for other macroscopic tumors investigated after i.v. administration of radiolabeled monoclonal antibodies, where T/B ratios usually were less than 10 (e.g. (16–22)). With MC tumors and ^{111}In-labeled octreotide a T/B ratio of about 100 can be expected. For one patient with EPT (Patient 7) the T/B was 1500. To our knowledge, this is the highest T/B ratio reported for a surgically excised macroscopic tumor investigated after preoperative injection of a radiolabeled substance. This was a benign islet cell tumor, located in the cystic duct. It had a positive immunoreaction with chromogranin A and the tumor cells contained argyrophilic granulae. This patient had a MEN I syndrome and had previously been operated on for an insulinoma in 1972 and a gastrinoma of the pancreas 9 yr later. A fraction of the radiopharmaceutical, although small, is excreted to the intestines via the biliary system. We have observed two patients with high bile-to-blood ratios Patients 86 and 260. An islet cell tumor located in the biliary tree is exposed to a higher concentration of radiopharmaceutical, or radionuclide, in surrounding fluids (blood and bile) than a similar tumor located in the pancreas (blood only). This could contribute to the extremely high T/B ratio observed in Patient 7, even if high density of somatostatin receptors and firm binding of the radiopharmaceutical probably is the main reason for this extremely high value. The T/B ratio obtained for the benign insulinoma of the head of the pancreas of the other patient with EPT (Patient 6) was only 6.3.

Varying density and different types of somatostatin receptors most probably cause different concentrations of ^{111}In-octreotide in tumors within the same patient and amongst different patients. Tumor size may also influence the variation in radioactivity concentration. In some studies on mice, the concentration of radiolabeled monoclonal antibodies decreased with increasing tumor size (23–26), probably due to reduced perfusion and presence of necrotic areas in larger tumors. A similar relationship has been shown in humans (18). In this study, with a limited number of tumors from each patient and relatively small tumors without necrotic areas weighing less than 15 g, the

concentration of ^{111}In-DTPA-D-Phe1-octreotide in tumor tissue was not influenced by the tumor size (Fig. 1).

The high tumor-to-(normal tissue) activity concentration ratios obtained in some of the patients in this study indicate the possibility to use radiolabeled octreotide for tumor therapy. Tumor-to-(normal tissue) ratios might be further increased by simultaneous administration of unlabeled octreotide. Dörr et al. (27) have recently reported enhanced visualization of liver metastases and reduced uptake in the spleen, liver and kidneys in five patients during ongoing octreotide therapy with 60 times higher amount of unlabeled octreotide. Experimental data for radioiodine-labeled Tyr^3-octreotide in rats have, however, shown a reduced uptake in tumor tissue after pretreatment with a larger (300–1000 times higher) amount of unlabeled octreotide (28,29). Further studies are necessary to find the amount of unlabeled octreotide for pretreatment for optimal tumor-to-(normal tissue) ratios of radiolabeled octreotide. The observed high concentration in bile may lead to unwanted high absorbed dose in the gall bladder and the gastrointestinal tract which could probably be reduced by increased gall bladder emptying and the use of laxatives during the treatment. Further studies of methods to enhance the tumor-to-(normal tissue) activity concentration ratios are needed.

Another important issue is the choice of radionuclide which depends on the macroscopic and microscopic distribution of the radiopharmaceutical in the tumor and in the normal tissues. The most suitable range of particles emitted from the radionuclide depends on the distribution at the cellular level. Radionuclides emitting radiation with penetrations less than the cell radius (or diameter) must be internalized into the cell to cause lethal damage. With a somewhat greater penetration it is sufficient if the radionuclides are bound to the cell membrane or extracellularly distributed. Large solid tumors with a heterogeneous uptake require radionuclides emitting β-radiation with ranges of about 1 cm (e.g., ^{90}Y or ^{186}Re). For smaller tumors with possibly a more homogeneous uptake it may be more suitable to use radionuclides which emit alpha particles or low-energy electrons. New radiolabeling methods have to be developed permitting other radionuclides than ^{111}In to be attached to the octreotide molecule.

Further work is also needed to collect detailed pharmacokinetic data from radiolabeled octreotide in man. The radionuclide activity concentration must be followed in various normal tissues and tumors by gamma camera measurements, during several days after injection, in a large patient material. Data obtained from surgical specimens, as in this study, are essential, especially regarding tissues impossible to measure with a gamma camera, to define the risk organs which will be dose limiting during potential therapy with radiolabeled octreotide. For a definite evaluation of a tumor therapy, the cumulated activities and absorbed doses in tumors and risk organs have to be estimated individually for each patient.

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