20. Rossetti C, Vanoli G, Paganelli G, et al. Human biodistribution, dosimetry, and clinical use of technetium(III)-99m-Q12. *J Nucl Med* 1994;35:1571–1580.
21. Crankshaw CL, Marmion M, Burleigh BD, Deutch E, Piwnica-Worms D. Nonreducible mixed ligand Tc(III) cations (Q complexes) are recognized as transport substrates by the human multidrug resistance (MDR) P-glycoprotein [Abstract]. *J Nucl Med* 1995;36(suppl):130P.
22. Schecter RL, Woo A, Duong M, Batist G. In vitro and in vivo mechanisms of drug resistance in rat mammary carcinoma model. *Cancer Res* 1991;51:1434–1442.
23. Luker G, Crankshaw CL, Marmion M, Burleigh BD, Deutsch E, Piwnica-Worms D. Mixed ligand Tc-99m(III) cations (Q-complexes) are recognized as transport substrates by the human multidrug resistance P-glycoprotein [Abstract]. *Proc Am Assoc Cancer Res* 1996;37:317.

Radiation Dosimetry for Indium-111-Pentetreotide

M.G. Stabin, P.P.M. Kooij, W.H. Bakker, T. Inoue, K. Endo, J. Coveney, R. de Jong and A. Minegishi
Oak Ridge Institute for Science and Education, Oak Ridge, Tennessee; University Hospital Dijkzigt, Rotterdam, The Netherlands; Gunma University, Gunma, Japan; Mallinckrodt, Inc., St. Louis, Missouri; Mallinckrodt Medical, B.V., Petten, Holland; IBRD Japan Corporation, Tokyo, Japan

We present radiation dose estimates for ^{111}In-pentetreotide. **Methods:** Kinetic data were gathered in 10 subjects at two different sites. A compartmental model was used to fit the data, including retention, in three major organs and excretion. **Results:** The data were consistent for the subjects at both sites. The organ receiving the highest dose was the kidneys (0.52 mGy/MBq); the effective dose equivalent was 0.1 mSv/MBq, and the effective dose was 0.073 mSv/MBq. **Conclusion:** The results of this study provide the basis for evaluation of radiation safety of this drug.

Key Words: dosimetry; indium-111-pentetreotide; somatostatin receptors; brain

J Nucl Med 1997; 38:1919–1922

The molecule ^{123}I-tyrosine (Tyr) (*3*)-octreotide is a somatostatin receptor imaging agent for use in the scintigraphic localization of neuroendocrine tumors (*1*). A similar molecule, pentetreotide, has been successfully labeled with ^{111}In complexed to the diethylenetriamine pentaacetic acid (DTPA) molecule and shows improved clinical results when used to study this system (*2*), due to higher renal clearance relative to hepatobiliary clearance. This article presents the radiation dosimetry of ^{111}In-DTPA-labeled pentetreotide based on two separate human studies involving a total of 10 patients. All results from the two studies will be shown; we believe that the results are in agreement and that a combined result, using data from all 10 patients, is recommended to establish the radiation dosimetry of this agent. It is hoped that the data presented in this article will be useful to regulators, users and others in understanding the radiation dosimetry of this agent in adults. The extension of these results to children and pregnant women will be discussed briefly.

MATERIALS AND METHODS

Human studies were undertaken by the University Hospital Dijkzigt in Rotterdam, the Netherlands, and at Gunma University in Gunma, Japan. The study in Holland involved six subjects; the study in Japan involved four subjects. In each study, ^{111}In-DTPA pentetreotide was administered to the subjects in quantities typical of a clinical imaging study, and the subsequent retention and excretion was studied through a combination of quantitative gamma camera imaging and urine collection and analysis. Fecal analysis was performed in only four subjects; it was thought that this pathway would not be very significant. The modeling results and a limited number of analyzed samples predicted a fairly low average gastrointestinal (GI) tract clearance (around 0.5%–2%, see Results), which agreed with the impressions from the gamma camera images. The methods for imaging and image quantitation are described in other works (*3,4*), although the energy windows in the Bakker et al. study (*3*) were changed from those used for ^{123}I to ensure their appropriateness for ^{111}In imaging. Briefly, in the studies conducted in the Netherlands, planar images were obtained with a large field of view camera equipped with a parallel-hole collimator. Anterior and posterior whole-body scintigrams were taken at 30 min postinjection, and again at 4 and 24 hr, and, in some cases, at 48 hr. Radioactivity in the blood, urine and feces was collected at various intervals over the course of the study, up to 48 hr, and measured in either a dose calibrator or a GeLi detector system. In the Japanese studies, anterior and posterior images were taken at 30 min and at 1, 2, 4, 6, 24 and 48 hr postinjection. Whole-body and SPECT imaging was performed using a gamma camera equipped with a medium-energy collimator. A 20% energy window centered at 173 and 247 keV was used. Geometric means of the anterior and posterior counts in regions of interest over the major organs were calculated. Urine samples were also collected at various times over the course of the study (to 48 hr) and analyzed in a dose calibrator.

Time-activity data gathered in the human studies were expressed as a percent of the administered activity and fit with a compartment model (Fig. 1) using the Simulation, Modeling and Analysis (SAAM) software (*5*). This model, when solved, is meant only to be descriptive of the observed kinetics of this agent for the purpose of developing radiation dose estimates. It generally provides two compartments to represent most organs and has two pathways for handling excretion (urinary and fecal). Areas under the time-activity curves for most organs were estimated directly from the fitted functions integrated over time and expressed as residence times (*6*). In the case of the urinary bladder, the program fit the cumulative urine activity curve, and then the bladder was assumed to void every 4.8 hr. The residence time for the bladder was then integrated from the time-activity curve assuming this voiding pattern. Activity entering the GI tract was assumed to clear through the gallbladder, small intestine, upper large intestine and lower large intestine according to the kinetics, as published previously (*7*).

Absorbed dose estimates were calculated using the standard MIRD technique (*6*), implemented in the MIRDOSE 3.1 computer software (*8*). The effective dose equivalent, as defined in ICRP Publication 30 (*7*), and the effective dose, as defined in ICRP Publication 60 (*9*), are shown in the tables. There is currently some

Received Feb. 15, 1996; revision accepted Feb. 21, 1997.
For correspondence or reprints contact: Michael G. Stabin, PhD, Oak Ridge Institute for Science and Education, P.O. Box 117, Oak Ridge, TN 37831-0117.

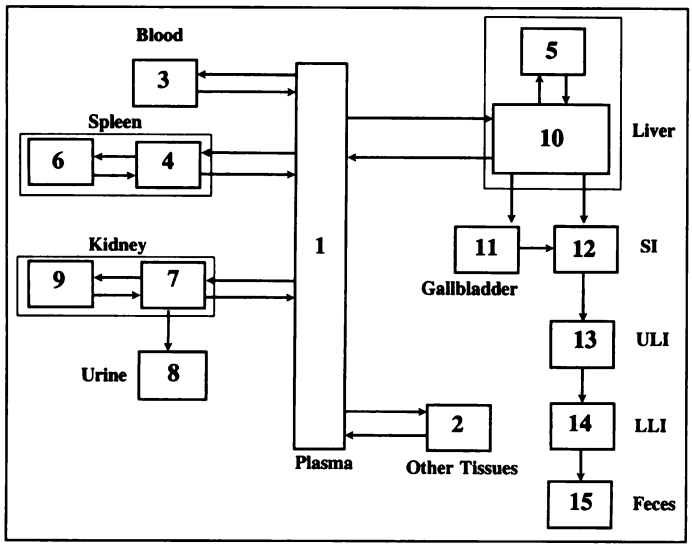

FIGURE 1. Compartmental model used for kinetic analysis. See text (Materials and Methods) for details.

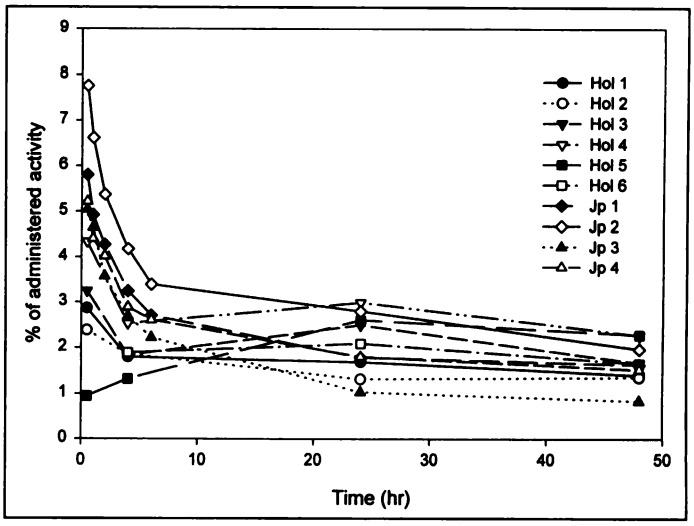

FIGURE 3. In-111-Pentetreotide activity in the liver as a function of time postadministration.

controversy about the use of these concepts (*10,11*), but they are given here for discussion purposes.

RESULTS

Measured activity in the spleen, liver, kidneys and urine are shown in Figures 2–5. Fecal excretion was measured in four patients at the Holland site. Total excretion was between 0.5% and 2.0% of the administered activity. Therefore, the amount of activity entering the GI tract was limited to values of only a few percent or so and were fit to observed values where available. The residence times for the various organs are shown in Table 1. Absorbed dose estimates calculated using the average residence times are shown in Table 2.

DISCUSSION

It can be seen from Table 1 and from Figures 2–5 that data from the two sites are in fairly good agreement. The kidney uptakes appear to be generally lower in the Japanese data at times longer than 2 hr, although the initial uptakes are all quite similar (with the exception of the one highest uptake). The kidney residence times for the Japanese appear to be lower for the four Japanese subjects compared to the six subjects from Holland; this trend appears also to be seen in the urinary bladder residence times, although not as strongly.

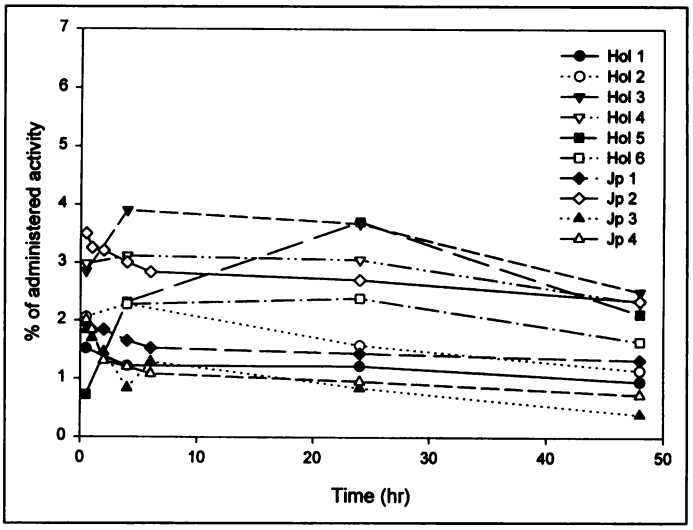

FIGURE 4. In-111-Pentetreotide activity in the spleen as a function of time postadministration.

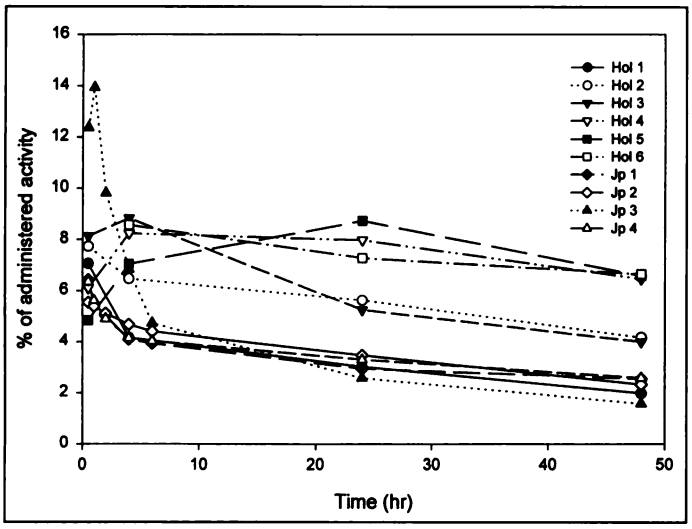

FIGURE 2. In-111-Pentetreotide activity in the kidneys as a function of time postadministration.

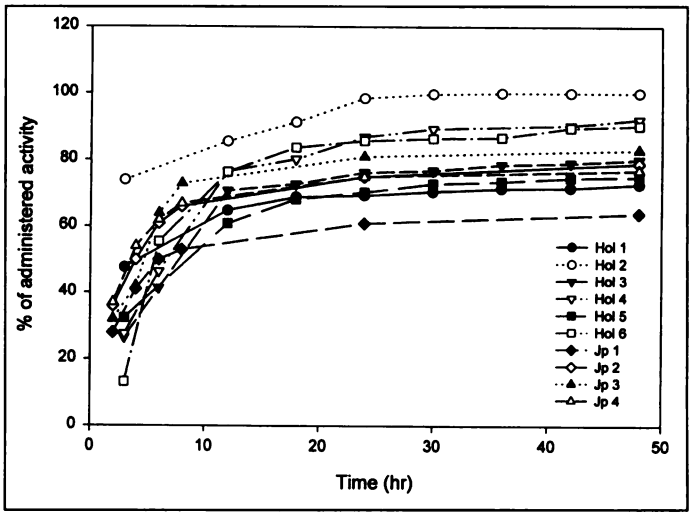

FIGURE 5. In-111-Pentetreotide activity in cumulative urinary excretion as a function of time postadministration.

TABLE 1
Organ Residence Times for Indium-111 Pentetreotide

Study no.	Gall bladder contents	LLI contents	Small intestine	ULI contents	Kidneys	Liver	Spleen	Urinary bladder contents	Remainder
Hol-1	0.025	0.588	0.138	0.396	5.19	1.58	2.08	3.18	3.16
Hol-2	0.025	0.36	0.085	0.243	5.83	1.13	1.25	3.40	5.4
Hol-3	0.017	0.303	0.071	0.204	6.28	1.46	1.77	3.21	11.3
Hol-4	0.016	0.297	0.070	0.20	4.46	0.917	0.89	3.39	6.84
Hol-5	0.018	0.429	0.101	0.29	3.85	1.16	1.84	2.98	10.1
Hol-6	0.016	0.371	0.087	0.25	2.36	1.0	0.67	3.38	12.0
Jp-1	0.0046	0.112	0.0263	0.0757	2.15	1.5	1.2	2.24	14.1
Jp-2	0.0135	0.344	0.0809	0.232	1.96	1.78	2.11	2.34	10.1
Jp-3	0.0056	0.134	0.0316	0.0906	1.72	0.876	0.386	2.27	14.2
Jp-4	0.0333	0.815	0.191	0.549	2.14	1.33	0.641	2.3	11.2
Mean	0.017	0.38	0.088	0.25	3.59	1.27	1.28	2.87	9.84
Std. dev.	0.0088	0.21	0.048	0.14	1.74	0.30	0.63	0.52	3.64

LLI = lower large intestine; ULI = upper large intestine.

The results overall appear to be consistent with each other and to build a good picture of the kinetics of this agent. Table 2 shows that the organs receiving the highest doses based on these data are the kidneys (0.52 mGy/MBq), urinary bladder wall (0.35 mGy/MBq) and spleen (0.34 mGy/MBq), with lower doses being received by the adrenals, gallbladder wall, ULI wall, liver and uterus (around 0.06 mGy/MBq). The effective dose equivalent and effective dose predicted by these dose estimates are similar, 0.1 and 0.073 mGy/MBq, respectively. As noted in Table 2, the quantity "total body dose" is considerably lower than either the effective dose equivalent or effective dose (by a factor of 2–3). As noted by Toohey and Stabin (*12*), this is a trend commonly observed for radiopharmaceuticals. In situations in which a nuclide selectively locates in a few organs (as is the goal of the use of nuclear medicine agents), the "total body dose" tells little about the real doses or risks involved, and it should not be used in risk-based decision making.

TABLE 2
Organ Radiation Dose Estimates for Indium-111 Pentetreotide

Organ	Estimated radiation dose	
	mGy/MBq	rad/mCi
Adrenals	6.0E−02	2.2E−01
Brain	1.4E−02	5.1E−02
Breasts	1.4E−02	5.1E−02
Gallbladder wall	5.3E−02	2.0E−01
LLI wall	8.4E−02	3.1E−01
Small intestine	4.4E−02	1.6E−01
Stomach	4.1E−02	1.5E−01
ULI wall	5.6E−02	2.1E−01
Heart wall	2.6E−02	9.6E−02
Kidneys	5.2E−01	1.9E+00
Liver	6.5E−02	2.4E−01
Lungs	2.3E−02	8.5E−02
Muscle	2.6E−02	9.7E−02
Ovaries	4.7E−02	1.7E−01
Pancreas	6.3E−02	2.3E−01
Red marrow	2.9E−02	1.1E−01
Bone surfaces	3.5E−02	1.3E−01
Skin	1.4E−02	5.3E−02
Spleen	3.4E−01	1.3E+00
Testes	2.7E−02	1.0E−01
Thymus	1.8E−02	6.8E−02
Thyroid	1.7E−02	6.3E−02
Urinary bladder wall	3.5E−01	1.3E+00
Uterus	6.5E−02	2.4E−01
Total body	3.0E−02	1.1E−01
Effective dose equivalent	1.0E−01 mSv/MBq	3.8E−01 rem/mCi
Effective dose	7.3E−02 mSv/MBq	2.7E−01 rem/mCi

LLI = lower large intestine; ULI = upper large intestine.

Given an administration of 111 MBq (3 mCi) of this compound, the absorbed dose to the kidneys would be around 57 mGy, about 39 mGy to the bladder wall and about 38 mGy to the spleen; the effective dose equivalent and effective dose predicted are around 11 and 8 mSv, respectively. The absorbed dose to the bladder wall may be further reduced by more frequent voiding than the value of 4.8 assumed in this model. We also analyzed the dose contribution from the potential contaminant $^{114m}In/^{114}In$ (assumed to be in secular equilibrium). Assuming a contaminant level of 0.25% at the time of administration, the $^{114m}In/^{114}In$ would contribute another 0.2% to 5.1% to the dose to any organ (the 5.1% contribution was to the kidneys) and would increase the effective dose or effective dose equivalent by approximately 3%.

We also evaluated the radiation doses to be expected in children (Table 3) and in pregnant women. These doses were also calculated with the MIRDOSE 3.1 software (*8*). There are currently no data available on the possible placental crossover of this agent. Assuming no placental crossover, the absorbed dose to the fetus in early pregnancy is estimated to be 0.078 mGy/MBq (0.29 rad/mCi), at 3 mo gestation 0.057 mGy/MBq (0.21 rad/mCi), at 6 mo gestation 0.033 mGy/MBq (0.12 rad/mCi) and at 9 mo gestation 0.029 mGy/MBq (0.11 rad/mCi).

The radiation doses expected from the use of this agent [assuming, for example, an administered activity of 111 MBq (3 mCi)] will be within the range of several other radiological and nuclear medicine procedures. Unlike with iodinated Tyr-3-octreotide, there is not the significant potential for high thyroid uptake and radiation dose. We performed an analysis, however, of the potential doses to the thyroid and pituitary gland, assuming uptakes of 0.03% and 0.003%, respectively (*13*), with removal only by radioactive decay. The estimated thyroid dose was 0.055 mGy/MBq, and that to the pituitary gland (assumed to be a sphere of mass 1 g) was 0.076 mGy/MBq.

Another consideration in the dosimetry of this agent is the potential dose to cellular substructures from the Auger electrons of ^{111}In should the molecule be internalized by the cell. There is evidence that this compound indeed crosses the cell membrane (*13*). Thus, future determinations of methods for calculating and understanding subcellular dose estimates may cause

TABLE 3
Radiation Dose Estimates for Adults and Children of Various Ages for Indium-111 Pentetreotide

Organ	Estimated radiation dose (mGy/MBq)					
	Adult	15-yr-old	10-yr-old	5-yr-old	1-yr-old	Newborn
Adrenals	6.0E−02	7.7E−02	1.2E−01	1.8E−01	3.2E−01	6.5E−01
Brain	1.4E−02	1.7E−02	2.8E−02	4.6E−02	8.1E−02	1.9E−01
Breasts	1.4E−02	1.8E−02	2.7E−02	4.2E−02	7.9E−02	1.8E−01
Gallbladder wall	5.3E−02	6.5E−02	9.5E−02	1.5E−01	2.4E−01	5.5E−01
LLI wall	8.4E−02	1.0E−01	1.7E−01	2.6E−01	4.7E−01	1.1E+00
Small intestine	4.4E−02	5.6E−02	8.8E−02	1.3E−01	2.3E−01	4.9E−01
Stomach	4.1E−02	4.9E−02	7.7E−02	1.1E−01	1.8E−01	3.9E−01
ULI wall	5.6E−02	7.1E−02	1.1E−01	1.8E−01	3.1E−01	6.9E−01
Heart wall	2.6E−02	3.3E−02	5.0E−02	7.4E−02	1.3E−01	2.8E−01
Kidneys	5.2E−01	6.2E−01	8.5E−01	1.2E+00	2.1E+00	5.0E+00
Liver	6.5E−02	8.4E−02	1.2E−01	1.7E−01	3.0E−01	6.4E−01
Lungs	2.3E−02	3.1E−02	4.5E−02	7.0E−02	1.3E−01	2.8E−01
Muscle	2.6E−02	3.2E−02	4.9E−02	7.4E−02	1.4E−01	3.0E−01
Ovaries	4.7E−02	6.1E−02	9.2E−02	1.4E−01	2.5E−01	5.0E−01
Pancreas	6.3E−02	7.6E−02	1.1E−01	1.7E−01	2.8E−01	5.7E−01
Red marrow	2.9E−02	3.4E−02	5.0E−02	7.0E−02	1.1E−01	2.3E−01
Bone surfaces	3.5E−02	4.3E−02	6.4E−02	9.6E−02	1.9E−01	4.2E−01
Skin	1.4E−02	1.7E−02	2.7E−02	4.3E−02	8.0E−02	1.9E−01
Spleen	3.4E−01	4.7E−01	7.1E−01	1.1E+00	1.9E+00	4.6E+00
Testes	2.7E−02	3.6E−02	6.0E−02	9.4E−02	1.8E−01	3.7E−01
Thymus	1.8E−02	2.3E−02	3.5E−02	5.5E−02	9.8E−02	2.2E−01
Thyroid	1.7E−02	2.2E−02	3.4E−02	5.6E−02	1.0E−01	2.3E−01
Urinary bladder wall	3.5E−01	4.4E−01	6.4E−01	9.4E−01	1.7E+00	3.9E+00
Uterus	6.5E−02	8.0E−02	1.3E−01	1.9E−01	3.3E−01	6.7E−01
Total body	3.0E−02	3.7E−02	5.6E−02	8.6E−02	1.6E−01	3.5E−01
Effective dose equivalent*	1.0E−01	1.3E−01	1.9E−01	2.8E−01	5.0E−01	1.1E+00
Effective dose*	7.3E−02	9.1E−02	1.3E−01	2.0E−01	3.5E−01	7.9E−01

*mSv/MBq.
LLI = lower large intestine; ULI = upper large intestine.

a re-evaluation of the dosimetry of this agent. However, these methods are still under discussion, and an analysis of them will not be attempted here.

CONCLUSION

The comprehensive study of the biokinetics and radiation dosimetry of ^{111}In- pentetreotide presented in this article should provide the basis for evaluation of this drug from the standpoint of radiation safety.

ACKNOWLEDGMENTS

This work was performed for the U.S. Department of Energy (DOE) under contract DE-AC05–76OR00033 and for the U.S. Food and Drug Administration (FDA) under Interagency Agreement No. FDA 224-75–3016, DOE 40-286-71.

The submitted article has been authored by a contractor of the U.S. government under contract DE-AC05–76OR00033. Accordingly, the U.S. government retains a nonexclusive, royalty-free license to publish or reproduce the published form of the contribution, or allow others to do so, for U.S. government purposes.

REFERENCES

1. Kwekkeboom D, van Urk H, Pauw KHB, et al. Octreotide scintigraphy for the detection of paragangliomas. *J Nucl Med* 1993;34:873–878.
2. Jamar F, Fiasse R, Leners N, Pauwels S. Somatostatin receptor imaging with indium-111-pentetreotide in gastroenterpancreatic neuroendocrine tumors: safety, efficacy and impact on patient management. *J Nucl Med* 1995;36:542–549.
3. Bakker W, Krenning E, Breeman W, et al. In vivo use of a radioiodinated somatostatin analog: dynamics, metabolism and bindng to somatostatin receptor-positive tumors in man. *J Nucl Med* 1991;32:1184–1189.
4. Inoue T, Ootake H, Hirano T, et al. Clinical evaluation of safety, pharmacokinetics and dosimetry of the somatostatin analog ^{111}In-DTPA-D-Phe-Octreotide. Report of the Phase I study. *Kaku Igaku* 1995;32:511–521.
5. Robertson J. *Compartmental distribution of radiotracer*. New York: CRC Press, 1983:73–142.
6. Loevinger R, Budinger T, Watson E. *MIRD primer for absorbed dose calculations*. Reston, VA: Society of Nuclear Medicine; 1988:1–10.
7. International Commission on Radiological Protection. *Limits for intakes of radionuclides by workers*. ICRP Publication 30. New York: Pergamon Press; 1979:5–6, 30–34.
8. Stabin M. MIRDOSE: the personal computer software for internal dose assessment in nuclear medicine. *J Nucl Med* 1996;37:538–546.
9. International Commission on Radiological Protection. *1990 recommendations of the international commission on radiological protection*. ICRP Publication 60. New York: Pergamon Press;1991:68.
10. Poston. Application of the effective dose equivalent to nuclear medicine patients. *J Nucl Med* 1993;34:714–716.
11. Stabin M, Stubbs J, Watson E. Recent controversy in radiation dosimetry. *Eur J Nucl Med* 1993;20:371–372.
12. Toohey R, Stabin M. Comparative analysis of dosimetry parameters for nuclear medicine. In: *Proceedings of the sixth international radiopharmaceutical dosimetry symposium*, 1997: in press.
13. Krenning E, Kooij P, Bakker W, et al. Radiotherapy with a radiolabeled somatostatin analog, [111In-DTPA-Phe1]-octreotide. A case history. *Ann NY Acad Sci* 1994;733: 496–506.