Radiation Dosimetry of Iodine-123 HEAT, an Alpha-1 Receptor Imaging Agent

Kathleen D. Thomas, David M. Greer, Margaret W. Couch, and Clyde M. Williams

Veterans Administration Medical Center and Department of Radiology, University of Florida, Gainesville, Florida

Biologic distribution data in the rat were obtained for the alpha-1 adrenoceptor imaging agent (±) 2-[β-(iodo-4-hydroxyphenyl)ethylaminomethyl] tetralone (HEAT) labeled with [^{125}I]. The major excretory routes were through the liver (67%) and the kidney (33%). Internal radiation absorbed dose estimates to nine source organs, total body, the GI tract, gonads, and red bone marrow were calculated for the human using the physical decay data for [^{123}I]. The critical organ was found to be the lower large intestine, receiving 1.1 rad per mCi of [^{123}I]HEAT administered. The total-body dose was found to be 58 mrad per mCi.

J Nucl Med 28:1745–1750, 1987

A drug that has antihypertensive properties in animals is 2-[β-(iodo-4-hydroxyphenyl)ethylaminomethyl] tetralone (HEAT) (*1,2*). These properties are based primarily on peripheral and central α-adrenoceptor antagonism (*3*). HEAT was subsequently found to be 140 times more selective for α_1-adrenoceptors than for α_2-adrenoceptors (*4,5*). HEAT has no activity on β-adrenoceptors and slight antagonism for serotonin and dopaminergic receptors. In 1981, two groups independently synthesized iodine-125 (^{125}I) HEAT and found that it had a higher affinity for the α_1-adrenoceptor than did the noniodinated parent compound (*6,7*). The two groups found K_D values of 78 and 25-150 pmol for α_1-adrenoceptors in rat cerebral cortex. These values are approximately tenfold higher than for the parent compound HEAT. Iodine-125 HEAT has proven to be a superior ligand for the mapping of α_1-adrenoceptor by autoradiography (*8–11*) yielding a very specific distribution of [^{125}I]HEAT binding sites in the brain of the rat with high concentrations in the thalamus and frontal cortex. Recently, intravenously administered [^{125}I]HEAT was also shown to cross the blood-brain barrier in the rat and concentrate in the thalamus and frontal cortex (*12*). For these reasons, [^{123}I]HEAT is an appropriate ligand for the in vivo imaging of α_1-adrenoceptors in humans by single photon emission computed tomography. The purpose of this paper is to estimate the radiation absorbed dose to humans from the use of [^{123}I]HEAT for the purpose of imaging α_1-adrenoceptors in the thalamus and frontal cortex of the brain.

Received Nov. 4, 1986; revision accepted May 15, 1987.

For reprints contact: Kathleen D. Thomas, Office of the Director (002A), Veterans Administration Medical Center, Gainesville, FL 32602.

MATERIALS AND METHODS

Radiopharmaceutical Preparation

(±)-β-([^{125}I]-Iodo-4-hydroxyphenyl) ethylaminomethyl]tetralone ([^{125}I]HEAT) in ethanol:0.001*M* KH_2PO_4 (1:1) was obtained commercially*: specific activity, 2,200 Ci/mmol; 100 μCi/ml. Radiochemical purity was checked by thin layer chromatography both before and after the experiments and was found to be >99%. (Solvent system 1 silica gel MeOH:$CHCl_3$ (3:5), Rf 0.73 (literature *(7)* 0.85); solvent system 2 cellulose, 0.05*M* ammonium formate, pH 8.4, Rf 0.030 (literature *(7)* 0.037).

Animal Test System for Tissue Distribution

Sixteen mature male Sprague-Dawley rats weighing 200 ± 8 g (mean ± s.d.) being fed a regular diet comprised the animal test system. A dose of 10 μCi of [^{125}I]HEAT (2 ng in 100 μl) was administered to each rat through the tail vein at time zero. The rats were housed in metabolic cages, which facilitated separate collection of urine and feces prior to killing at 1, 3, 24, and 48 hr intervals postinjection. Four of the 16 rats were killed by intraperitoneal injection of a lethal dose (1 g) of sodium pentobarbital at each successive time interval, and nine tissues were obtained. The urine, feces, and tissue samples were placed in thin-walled plastic vials, weighed and counted in a shielded sodium iodide crystal well gamma counter system.† Each sample was counted long enough to achieve a s.e. of <2.4%. The radioconcentrations were expressed as percent injected dose per gram (Table 1) and percent injected dose per organ (Table 2). All values in Tables 1 and 2 were decay corrected to the time of administration (t = 0) of the [^{125}I]HEAT.

TABLE 1
Biodistribution of [^{125}I]HEAT in Normal Rats (N = 4) (Mean Percent Injected Dose per Gram ± s.e.m.)

Organ	1 hr	3 hr	24 hr	48 hr
Adrenals	0.79 ± 0.40	0.77 ± 0.56	0.07 ± 0.03	0.04 ± 0.01
Blood	0.14 ± 0.04	0.11 ± 0.01	0.03 ± 0.01	0.01 ± 0.00
Brain	0.19 ± 0.06	0.11 ± 0.01	0.02 ± 0.01	0.003 ± 0.000
Heart	0.46 ± 0.10	0.11 ± 0.01	0.02 ± 0.01	0.01 ± 0.00
Kidneys	0.60 ± 0.15	0.27 ± 0.01	0.09 ± 0.03	0.02 ± 0.00
Liver	0.57 ± 0.13	0.38 ± 0.02	0.07 ± 0.02	0.02 ± 0.01
Lungs	1.68 ± 0.40	0.48 ± 0.03	0.05 ± 0.01	0.02 ± 0.00
Spleen	0.67 ± 0.22	0.47 ± 0.25	0.04 ± 0.02	0.02 ± 0.00
Testes	0.08 ± 0.04	0.13 ± 0.01	0.02 ± 0.00	0.01 ± 0.00
Thyroid	5.9 ± 1.6	20 ± 2	82 ± 18	22 ± 4

Biodistribution of [^{125}I]HEAT

The biodistribution of [^{125}I]HEAT is shown in Tables 1 and 2. The major excretory routes were through the liver and kidneys, 90% of the administered radioactivity being excreted within 48 hr (Table 3). The results are in good agreement with earlier work with carbon-14 HEAT in which 96% of the radioactivity was excreted in 60 hr (*13*).

Conversion of Animal to Human Data

The conversion from animal data to the human model was carried out by multiplying the % injected dose per g of the rat organ times the total mass of the rat whole body (kg). The % kg per g of the animal was then multiplied by the ratio of the standard man organ mass (*14,15*) in g to the 70 kg reference man whole-body mass. This conversion yields % injected dose per human organ (*16*). The conversion was used for the following source organs: brain, heart wall, kidneys, liver, lungs, spleen, and testes. The conversion was not carried out for the adrenal and thyroid source organs because of their comparatively smaller organ masses. Thus the animal values for % injected dose per organ were assumed to apply directly to the human model.

Calculation of Source Organ Biologic and Effective Half-Lives and Intercept Values

The biologic half-life ($T_{½}$) and intercept, the % injected dose per organ at time zero, parameters for the adrenals, brain, heart wall, kidneys, liver, lungs, spleen, testes, and thyroid were calculated by using a software package developed at Oak Ridge Associated Universities. The program is entitled "MIRDOSE" (*17*) and was executed on a personal microcomputer.‡ The % injected dose per organ data versus time for each source organ were entered into the "PLOT" routine of the "MIRDOSE" program. The "PLOT" program analyzes the data using linear or nonlinear least squares technique to fit the retention data to either a one- or two-compartment exponential function, respectively. The bioretention data for the adrenals, brain, heart wall, kidneys, liver, lungs, and spleen were best fit by a curve comprised of two single exponential compartments, one short-lived and one long-lived. The bioretention data for the testes were best fit by a one-compartment exponential curve. In order to fit the thyroid retention data, the increase in uptake until the 24-hr data point was best described by a one-compartment exponential ingrowth curve. The decline in retention from 24 to 48 hr was best fit by a one-compartment exponential curve. The operator has the option to change the curve parameters to yield the best fit to the data. After the operator accepts the fit of the curve, the program prints out the biologic $T_{½}$ and the intercept value for each compartment.

The effective half-life, T_{eff}, for each compartment was calculated according to the following equation:

$$T_{eff} = \frac{T_B T_P}{T_B + T_P}, \quad (1)$$

where T_B is the biologic $T_{½}$ and T_P is the physical $T_{½}$ of ^{123}I. The T_{eff} and intercept values for the nine source organs are given in Table 4.

Calculation of Residence Times for the Adrenals, Brain, Heart Wall, Kidneys, Liver, Lungs, Spleen, Testes and Thyroid

The residence time, τ, for the first seven of the above nine source organs was calculated using the following equation:

TABLE 2
Biodistribution of [^{125}]HEAT in Normal Rats (N = 4) (Mean Percent Injected Dose per Organ ± s.e.m.)

Organ	1 hr	3 hr	24 hr	48 hr
Adrenals	0.03 ± 0.01	0.02 ± 0.003	0.003 ± 0.001	0.002 ± 0.000
Brain	0.31 ± 0.09	0.20 ± 0.03	0.03 ± 0.01	0.02 ± 0.01
Heart	0.41 ± 0.10	0.09 ± 0.01	0.02 ± 0.01	0.01 ± 0.00
Kidneys	1.25 ± 0.41	0.50 ± 0.05	0.15 ± 0.05	0.03 ± 0.00
Liver	4.44 ± 1.18	3.53 ± 0.39	0.52 ± 0.16	0.08 ± 0.02
Lungs	1.76 ± 0.63	0.44 ± 0.03	0.05 ± 0.02	0.02 ± 0.00
Spleen	0.40 ± 0.16	0.24 ± 0.13	0.02 ± 0.01	0.01 ± 0.004
Testes	0.16 ± 0.05	0.27 ± 0.02	0.04 ± 0.005	0.04 ± 0.02
Thyroid	0.07 ± 0.03	0.31 ± 0.03	1.29 ± 0.23	0.43 ± 0.18
Total retention	8.84	5.60	2.12	0.64

TABLE 3
Excretion of [^{125}I]HEAT After Administration to Normal Sprague-Dawley Rats (N = 4) (Mean Percent Injected Dose ± s.e.m.)

Mode	1 hr	3 hr	24 hr	48 hr
Urine	5.0 (± 2.0)	13 (± 3)	30 (± 5)	31 (± 4)
Feces	0.0	0.0	50 (± 9)	59 (± 11)
Total	5	13	80	90

$$\tau = 1.443 \times [T_{effA} \times \text{intercept}_A + T_{effB} \times \text{intercept}_B], \quad (2)$$

where T_{effA} is the effective $T_{½}$ of the long-lived compartment, intercept_A is the intercept of the long-lived compartment, T_{effB} is the effective $T_{½}$ of the short-lived compartment, and intercept_B is the intercept of the short-lived compartment. The residence time calculated from Eq. (2) assumes that after the last datum point collected at 48 hr, the clearance curve is extrapolated to infinity with continued clearance at the T_B of the long-lived component. The residence time, τ, for the testes and thyroid gland were calculated using the following equation:

$$\tau = 1.443 \times T_{eff} \times f, \quad (3)$$

where T_{eff} and f are the effective $T_{½}$ and intercept, respectively, of the single compartment exponential curve.

Calculation of the Urinary Bladder Residence Time

The dynamic bladder model developed by Cloutier et al. (*18*) was used in the "MIRDOSE" program to calculate the urinary bladder residence time. The model assumes that the bladder fills and empties at regular intervals. The % urine

TABLE 4
Biologic Half-Lives, Effective Half-Lives, Intercepts, Correction Factors and Residence Times for 12 Source Organs and Remainder of Body

Organ	T_B (hr)		T_{eff} (hr)*		Intercept		Correction Factor	Residence time (hr)
	A (Long)	B (Short)	A (Long)	B (Short)	A (Long)	B (Short)		
Adrenals	41.3	2.0	9.94	1.73	4.5×10^{-5}	0.0004	—	0.0016
Brain	24.1	1.92	8.5	3.8	0.0004	0.00217	4.146	0.042
Heart wall	38.1	0.85	9.75	0.798	0.00028	0.00972	1.70	0.0257
Kidneys	16.5	1.02	7.3	0.95	0.0019	0.0081	0.886	0.0276
Liver	13.3	2.04	6.6	1.76	0.00244	0.0048	5.143	0.182
Lungs	18.1	0.961	7.6	0.90	.00125	0.0321	2.857	0.158
Spleen	33.5	3.6	9.42	2.82	0.00054	0.0075	0.5143	0.019
Testes	13.3		6.61		0.00102		0.10	0.001
Thyroid†	—	—	7.02	—	0.0129	—	—	Ingrowth area = 0.0749 Residence time (for T_{eff} = 7.02) is 0.131. Total = 0.131 ± 0.0749 = 0.206
Remainder of body	24.0	5.33	8.5	3.8	0.40	0.60	0.833	6.83
Small intestine	—	—	—	—	—	—	—	2.18
Upper large intestine	—	—	—	—	—	—	—	4.20
Lower large intestine	—	—	—	—	—	—	—	3.41

* T_{eff} was calculated using T_p = 13.1 hr for ^{123}I.

† Thyroid uptake reflects iodide ion rather than [^{125}I]HEAT. A separate imaging experiment in a rat pretreated with iodide (Lugol's solution) resulted in no thyroid uptake at 4 hr postinjection of [^{125}I]HEAT.

remaining in the body was calculated by subtracting the % excreted at each time interval from the % remaining at time zero, which in this case was 31%, taken from Table 3. The % remaining versus time data given in Table 5 were entered into the PLOT routine. The data were fit by a single exponential compartment with a biologic $T_{1/2}$ of 4.9 hr. The fraction of injected activity entering the bladder at time zero is equal to the ratio of % excreted through the urine at the end of data collection to the total % injected dose excreted. In this case at 48 hr postinjection, the ratio is 31%/90% or 0.34 of the injected dose would eventually be passed through the urine excretion route. In order to estimate the maximum bladder dose to the human, the voiding interval of 4.8 hr was used, which assumes that in a 24-hr time period the average person voids five times.

Calculation of Gastrointestinal Tract Source Organ Residence Times

The calculations of the residence times for the GI tract source organs are based on the approximate expressions for the total number of transformations for each region of the GI tract given in ICRP 30 (*19*). The following assumptions were made prior to carrying out the calculations. The [^{125}I]HEAT compound is introduced into the small intestine through the common bile duct from the hepatic duct. The pathway into the small intestine was thus assumed to be 100% from the liver and 0% from the stomach, which was not considered a source organ. No feedback mechanisms were assumed to exist. After 48 hr postinjection of the [^{125}I]HEAT, 90% of the injected dose is excreted through the feces and urine. The fraction of the injected activity entering the small intestine through the liver is the ratio of % excretion through the feces divided by total excretion at 48 hr, in this case, 59%/90% or 0.66. The biologic rates of clearance for the small intestine, λ_{SI}, upper large intestine, λ_{ULI}, and the lower larger intestine, λ_{LLI}, were $\frac{1}{4}$ hr^{-1}, $\frac{1}{13}$ hr^{-1} and $\frac{1}{24}$ hr^{-1}, respectively, as given in Eve (*20*). The radioactive decay constant λ_R, is equal to $\ln 2/T_P$, where T_P equals 13.1 hr for ^{123}I. The residence times for the small intestine, upper large intestine and lower large intestine are given by:

$$\tau_{SI} = \frac{\text{fraction of injected activity entering S.I.}}{\lambda_R + \lambda_{SI}} \quad (4)$$

$$\tau_{ULI} = \frac{\tau_{SI}\,(\lambda_{SI})}{\lambda_R + \lambda_{ULI}} \quad (5)$$

$$\tau_{LLI} = \frac{\tau_{ULI}\,(\lambda_{ULI})}{\lambda_R + \lambda_{LLI}}. \quad (6)$$

The residence times calculated for the GI tract source organs are given in Table 4.

TABLE 5
Percent Injected Dose Remaining Versus Time Data Used to Calculate the Biologic Half-Life of Urinary Clearance of [^{125}I]HEAT

Time (hr)	% Injected dose remaining	% Injected dose excreted
0	31	0
1	26	5
3	18	13
24	1	30

Calculation of the Residence Time for the Remainder of the Body

The residence time for the labeled [^{125}I]HEAT taken up in the remainder of the body, excluding the 12 other source organs, was calculated using the following equation:

$$\tau_{RB} = 1.443\, f_R\, [T_{effA} \times \text{intercept}_A + T_{effB} \times \text{intercept}_B], \quad (7)$$

where f_R is the fraction of the injected dose retained in the remainder of the body. In order to generate the biologic clearance parameters for the remainder of the body, the percent injected dose retained in the body was generated by subtracting the total percent excreted data values given in Table 3 by 100%. The percent injected dose retained versus time data given in Table 6 were entered in the PLOT routine of the MIRDOSE program. The biologic $T_{1/2}$, effective $T_{1/2}$, and intercepts of the short- and long-lived compartments generated for the remainder of the body are given in Table 4.

The fraction retained, f_R, was determined by first summing the four subtotal percent injected dose values (given in the bottom line of Table 2) yielding a total of 17% retained in the organs listed in Table 2. This value is subtracted from 100% yielding the f_R value of 83% or 0.83.

Radiochemical Purity of [^{123}I]HEAT

For human use, it is desirable to use pure ^{123}I with no contamination from the long-lived ^{124}I, T_P equal to 4 days and ^{125}I, T_P equal to 60 days. For this reason, the best commercially available product is Ultrapure ^{123}I from Atomic Energy of Canada Ltd.[§] This vendor states that the ^{123}I is prepared from enriched ^{124}Xe by the reaction: ^{124}Xe (p,2n)$\rightarrow$^{123}Cs$\rightarrow$^{123}Xe$\rightarrow$ ^{123}I. The vendor also states that the final product contains no detectable ^{124}I or ^{125}I and trace amounts (0.03–0.05%) of the contaminant tellurium-121 (^{121}Te). A sample of the ultrapure ^{123}I from AECL was analyzed using a high purity germanium detector[¶] interfaced to a multichannel analyzer computer system[**] to detect the presence of trace amounts of the possible radiocontaminants. The analysis revealed no detectable ^{124}I and a ^{121}Te abundance of 0.005%, which is ten times less than the 0.05% abundance stated by the manufacturer.

RESULTS

Radiation Dose Estimates

The residence times given in Table 4 for the 11 source organs and the remainder of the body were entered into the "MIRDOSE" program. The program employs the

TABLE 6
Percent Injected Dose Remaining Versus Time Data Used to Generate the Biologic Clearance Parameters of [^{125}I]HEAT Remaining in the Whole Body

Time (hr)	% Injected dose remaining	% Injected dose excreted
0	100	0
1	95	5
3	87	13
24	20	80
48	10	90

methodology developed by the Medical Internal Radiation Dose (MIRD) Committee of The Society of Nuclear Medicine to determine the radiation absorbed dose to target organ(s) from a radionuclide distributed within several source organs (*21*).

The program can be set up to calculate absorbed doses to any of 25 target organs from any combination of 24 source organs. The program calculates "S" factors from stored tables of specific absorbed fractions for the MIRD adult male phantom (*15*) and decay data corresponding to the radionuclide chosen from the 59 available. The "MIRDOSE" program has also incorporated the excess cumulated activity correction proposed by Cloutier et al. (*22*) for calculating the radiation dose from the remainder of the body. This correction is necessary to avoid using the activity in the target twice when calculating the dose to the target organ from self-irradiation and the remainder of the body.

The radiation absorbed dose estimates per millicurie of [^{123}I]HEAT administered for the source organs, the GI tract, gonads, red bone marrow, and the total body are given in Table 7. Radiation absorbed dose estimates per millicurie of ^{123}I were calculated for the contaminant, ^{121}Te, using an abundance of 0.005%. The absorbed dose values ranged from a minimum of 1.0×10^{-6} rad per millicurie for the brain to a maximum of 6.8×10^{-5} rad per millicurie for the upper large intestine. These values were found to be only a fraction (no greater than 0.07%) of the dose estimates from ^{123}I given in Table 7. Thus the contaminant, ^{121}Te, does not contribute significantly to the total radiation absorbed dose estimates.

TABLE 7
Radiation Absorbed Dose Estimates per Millicurie of [^{123}I] HEAT Administered for Adult Human

Organ	rad/mCi
Lower large intestine	1.1
Upper large intestine	1.0
Red bone marrow†	0.91
Thyroid	0.80
Small intestine	0.46
Bladder wall*	0.24
Ovaries†	0.24
Kidneys	0.05
Liver	0.044
Spleen	0.040
Adrenals	0.035
Lungs	0.030
Testes	0.027
Heart wall	0.027
Brain	0.008
Total body*	0.058

* Calculated for 4.8 hr voiding interval.
† Ovaries and red bone marrow were not considered source organs.

DISCUSSION

The assumption made before using the scaled rat biodistribution data in estimating the radiation dose to the human was that [^{123}I]HEAT at a specific activity of 2.4×10^5 Ci/mmol will distribute in humans equivalent to the measured distribution of [^{125}I]HEAT at a specific activity of 2,200 Ci/mmol. In order to investigate the validity of this assumption, human excretion data will be collected from subjects participating in the phase I clinical trials of [^{123}I]HEAT.

The total absorbed dose to each organ will ultimately depend on the injected dose. Presently, it is difficult to predict what the optimum injected dose of [^{123}I]HEAT for α_1 imaging in humans will be until preliminary imaging experiments have been carried out with primates. However, excellent images of muscarinic receptors in humans have been obtained with 5 mCi doses of [^{123}I]QNB (*23*). Equally good images of dopamine (D-2) receptors have been made of the human brain with 3 mCi of [^{123}I]FLA-981 (*24*). If diagnostic quality images of α_1-adrenoceptors in the human brain can be obtained with 3–5 mCi, then it would be possible to keep the radiation absorbed dose to the critical target organ, the lower large intestine, within the conventional 5 rad per organ limit per single study (*25*). The dose to the thyroid can be significantly reduced by blocking the thyroid with Lugol's solution prior to administration of the [^{123}I]HEAT compound. The radiation absorbed dose to the urinary bladder can also be reduced by up to 40% by decreasing the patient voiding interval from 4.8 hr to 1.0 hr.

NOTES

* DuPont Company, No. Billerica, MA.
† Canberra, Meriden, CT.
‡ IBM Model XT Personal Computer, Armonk, NY.
§ Atomic Energy of Canada Limited, Ontario, Canada.
¶ E. G. & G. Ortec, Oak Ridge, TN.
** Tracor Northern, Austin, TX.

ACKNOWLEDGMENTS

The authors thank Michael G. Stabin at Oak Ridge Associated Universities Radiopharmaceutical Internal Dose Information Center for his invaluable assistance in using the MIRDOSE software program for this dosimetry application. The authors also thank the Enrivonmental Health and Safety Division of the University of Florida for the use of their personal computer system. The assistance of Ms. Linda Pigott in the preparation of this manuscript is greatly appreciated.

REFERENCES

1. Benthe HF, Göthert M, Tuchinda P. Noradrenalin-antagonistiche Wirkung verschiedener phenylethy-

lamin-und phenoxyaethylamin-derivate. *Arzneim Forsch* 1972; 22:1468–1474.
2. Benthe HF, Göthert M, Krug J. Beeinflussung der Wirkungsstarke von α-Rezeptorenblockern durch Reserpin. *Arzneim Forsch* 1975; 25:402–407.
3. Clineschmidt BV, Pflueger AB, Bunting PR, et al. Central catecholamine receptor blocking actions of BE-2254 ('HEAT'): comparison with chlorpromazine and haloperidol. *Eur J Pharmacol* 1975; 32:279–286.
4. Heinz N, Hofferber E. Zur Pharmackologie des α-rezeptoren-blockers BE2254 (HEAT). *Arzeim Forsch* 1980; 30:2135–2139.
5. Gothert M, Nolte J, Weinheimer G. Preferential blockade of postsynaptic α-adrenoceptors by BE2254. *Eur J Pharmacol* 1981; 70:35–42.
6. Engel G, Hoyer D. [^{125}I] BE-2254, a new high affinity radioligand for α_1-adrenoceptors. *Eur J Pharmacol* 1981; 73:221–224.
7. Glossman H, Lübbecke F, Belleman P. [^{125}I]-HEAT, a selective, high affinity, high specific activity ligand for alpha$_1$-adrenoceptors. *Nauyn-Schmiede Arch Pharmacol* 1981; 318:1–9.
8. Jones LS, Miller G, Gauger LL, et al. Regional distribution of rat brain alpha$_1$-adrenergic receptors: correlation between (^{125}I)-HEAT membrane binding and *in vitro* autoradiography. *Life Sci* 1985; 36:45–51.
9. Jones LS, Gauger LL, Davis JN. Anatomy of brain alpha$_1$-adrenergic receptors: *in vitro* autoradiography with [^{125}I]-HEAT. *J Comp Neurol* 1985; 231:190–208.
10. Jones LS, Gauger LL, Davis JN. Brain α_1-adrenergic receptors: suitability of [^{125}I]-HEAT as a radioligand for in vitro autoradiography. *Eur J Pharmacol* 1983; 93:291–292.
11. Unnerstall JR, Kuhar MJ. Mapping the alpha adrenergic receptor in the central nervous system: a guide to structure and function. 1986; in press.
12. O'Tuama LA, Frost JJ, Wilson AA, et al. In vivo labeling of alpha-1 adrenergic receptors with I-125 2-β(4-hydroxyphenyl)ethlaminomethyl-tetralone (HEAT) [Abstract]. *J Nucl Med* 1986; 27:969.
13. Hofferber E. BE-2254. *Drugs of the future* 1982; 7:231–234.
14. International Commission on Radiological Protection. Report of task group on reference man, ICRP Publication 23. New York: Pergamon Press, 1975.
15. Snyder WS, Ford MR, Warner GG. Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a heterogenous phantom. MIRD Pamphlet No. 5, revised. New York: The Society of Nuclear Medicine, 1978.
16. Roedler HD. Accuracy of internal dose calculations with special consideration of radiopharmaceutical biokinetics. Third Annual International Radiopharmaceutical Dosimetry Symposium, October 7–10, 1980, Oak Ridge, Tennessee, 1–20.
17. Watson EE, Stabin MG, Bolch WE. MIRDOSE. Oak Ridge Associated Universities, Oak Ridge, Tennessee, 1984.
18. Cloutier R, Smith S, Watson E, et al. Dose to the fetus from radionuclides in the bladder. *Health Phys* 1973; 25:147–161.
19. Committee 2 of the International Commission on Radiological Protection. ICRP Publication 30, Part 1: Limits for the Intakes of Radionuclides by Workers. New York: Pergamon Press, 1978.
20. Eve IS. A review of the physiology of the gastrointestinal tract in relation to radiation doses from radioactive materials. *Health Phys* 1966; 12:131–161.
21. Loevinger R, Berman M. A revised schema for calculating the absorbed dose from biologically distributed radionuclides. MIRD Pamphlet No. 1, revised. New York: The Society of Nuclear Medicine, 1976.
22. Cloutier R, Watson EE, Rohrer R, et al. Calculating the radiation dose to an organ. *J Nucl Med* 1973; 14:53–55.
23. Eckelman WC, Reba RC, Rzeszotarski WJ, et al. External imaging of cerebral muscarinic acetylcholine receptors. *Science* 1984; 223:291–293.
24. Crawley JCW, Smith T, Zanelli GD, et al. Dopamine receptors in the human brain imaged with a new ligand labelled with ^{123}I. *Clin Sci* 1986; 70 (suppl. 13) 53P.
25. Code of Federal Regulations. Title 21. Food and Drugs. Part 361, Prescription drugs for human use generally recognized as safe and effective and not misbranded: drugs used in research. U.S. Government Printing Office, Washington, DC, 1981, 161.