Human Biodistribution and Dosimetry of the SPECT Benzodiazepine Receptor Radioligand Iodine-123-Iomazenil

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SPECT imaging of the brain with [^{123}I]iomazenil has shown avid uptake of the radioligand in a distribution consistent with benzodiazepine receptor binding. The purposes of this study were to measure the whole-body distribution of activity following i.v. administration of [^{123}I]iomazenil and to evaluate the resulting organ radiation burdens. **Methods:** Serial total body scans were obtained in healthy volunteers after thyroid blockade and demonstrated avid brain uptake of radioligand. **Results:** Abdominal imaging showed significant activity retention within the urinary and gastrointestinal tracts consistent with excretion via these routes. Absorbed dose to the urinary bladder was calculated to be 0.19 mGy/MBq, to the lower large intestine 0.079 mGy/MBq, to the upper large intestine 0.066 mGy/MBq, and to the thyroid 0.063 mGy/MBq. **Conclusion:** Thyroid uptake may in part have represented binding to benzodiazepine receptors, since radioligand binding to tissue homogenates prepared from human thyroid showed the presence of benzodiazepine binding sites.

Key Words: iodine-123 iomazenil; dosimetry; benzodiazepine receptor

J Nucl Med 1994; 35:399–404

Carbon-11-flumazenil (or Ro 15-1788) and its iodinated analog [^{123}I]iomazenil (or Ro 16-0154) have been used to image benzodiazepine receptors in human brain (*1–7*). In comparison to [^{11}C]flumazenil, [^{123}I]iomazenil has a tenfold higher affinity for the neuronal type benzodiazepine receptor and slower brain washout (*7–10*). In addition, [^{123}I]iomazenil has a remarkably high brain uptake (approximately 10% of the injected dose in nonhuman primates) and a distribution consistent with that of benzodiazepine receptors (*7,9*). These studies confirm that [^{123}I]iomazenil has favorable in vivo imaging characteristics and that this agent may be useful in the evaluation of disease states where the function of benzodiazepine/GABA$_A$ receptors is abnormal.

Received Aug. 25, 1993; revision accepted Dec. 14, 1993.
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The application of SPECT imaging with [^{123}I]iomazenil to human subjects requires that the biodistribution and organ dosimetry of this radiopharmaceutical be well understood. The purposes of these experiments were to determine the whole-body distribution of radioactivity following the intravenous administration of [^{123}I]iomazenil and to use these data to estimate organ dosimetry.

MATERIALS AND METHODS

Radiosynthesis

Iodine-123-iomazenil and [^{125}I]iomazenil were prepared via oxidative radioiodination of the tributylstannyl precursor (ethyl 7-(tributylstannyl)-5,6dihydro-5-methyl-6-oxo-4H-imidazol[1,5a]-[1,4]benzodiazepine-3-carboxylate) using an iodination method described elsewhere (*11*). The specific activity was greater than the detectable limits of our UV system (i.e., >5,000 Ci/mmole). Using the same batch of precursor and identical methods, McBride et al. (*12*) measured the specific activity of the product at 180,000 Ci/mmole. The final product was formulated in sterile saline.

Subjects

Eight healthy volunteers (four males, four females, age 27 ± 5 yr; weight 73 ± 11 kg, expressed as mean ± s.e.m.) participated in the study. After informed consent had been obtained, each subject was premedicated with Lugol's solution (containing 5% iodine and 10% potassium iodide) to minimize thyroid uptake of radioiodide. Each subject received a blocking dose of approximately 0.5 ml Lugol's solution the day before and again on the morning of the experimental study at approximately 1 hr prior to radioligand injection.

Whole-Body Imaging

Whole-body transmission and emission scans were acquired on the Strichman 860 Whole Body Imager (Strichman Medical Equipment, Medfield, MA). This multicrystal, dual-headed rectilinear system provides simultaneous anterior and posterior images.

Transmission Scans. A whole-body transmission scan was obtained on each subject prior to radiotracer injection for attenuation correction of the subsequent emission images. Transmission scans were acquired by attaching a line source containing 1–2 mCi ^{99m}Tc to the posterior camera head and recording counts from the anterior head. Regions of interest (ROIs) were drawn on whole-

body images using software for the MacIntosh computer (Image 1.41). These regions included the brain, thyroid, lung, liver, intestine, kidneys and bladder, as well as a region outside the body (not attenuated). Transmission factors were calculated from the ratio of counts/pixel within each organ ROI to counts/pixel within the off-body region. The square root of each transmission factor provided organ attenuation correction factors that were applied to subsequent conjugate counts (*13*).

The decision to use ^{99m}Tc was based on a previous experiment in our laboratory that compared transmission factors derived from ^{99m}Tc and ^{123}I line sources in two subjects. Intrasubject comparison showed that ^{99m}Tc provided attenuation correction factors approximately 6% greater for all organs than did ^{123}I (Seibyl J, et al., unpublished data). The ^{99m}Tc derived attenuation factors were adjusted to account for this difference prior to correction of emission data.

Emission Scans. Whole-body emission scans were acquired following the bolus intravenous injection of 2.85 ± 0.20 mCi (mean ± s.e.m.) of [^{123}I]iomazenil. Imaging was begun immediately after injection and was performed every 30 min for 3 hr, then every 60 min for 3 hr, and again at 18 and 24 hr after tracer administration.

Urinary Excretion Data. Urinary excretion of tracer was estimated by quantification of activity present in urine samples collected every 6 hr during the first 24 hr following [^{123}I]iomazenil injection.

Image Data Analysis

Digital emission scans were transferred to a Macintosh computer for ROI analysis, with duplicate regions defined on anterior and posterior views. For each subject, the following ROIs were drawn on whole-body images of [^{123}I]iomazenil distribution: brain, thyroid, lung, liver, gallbladder, kidneys, bowel and bladder. These regions were drawn on every subject at each time point. Due to the inherent variability in drawing the small versus large intestine, a single bowel ROI was drawn to include both the small and large intestine. A single operator drew all ROIs on each subject, minimizing variability in region definition.

Individual organ uptake of ^{123}I was calculated using a standard conjugate counting paradigm (*13*). Calculations assumed that organ activity could be derived from ROI data using the product of anterior and posterior counts from the [^{123}I]iomazenil source. The square root of these conjugate counts was corrected for soft-tissue attenuation using the attenuation factors described above and was converted to microcurie activity by application of a conversion factor. This conversion factor was derived from a separate experiment in which a 3-mCi distributed pad source of ^{123}I was serially imaged with the Strichman 860 camera. The pad source was prepared at the time of patient dosing and was imaged each time the patient was imaged, i.e., every 30 min for 3 hr, every 60 min for 3 hr, at 18 and at 24 hr. Both the subject and pad source were imaged in rectilinear fashion using identical acquisition parameters. The square root of the conjugate counts from the anterior and posterior images of the pad source (geometric mean), divided by the known activity in the pad, provided a conversion factor in units of cps/μCi (*13*). Organ activity was then decay-corrected at each time point and expressed as a percentage of the administered dose of [^{123}I]iomazenil. Time-activity curves for each organ ROI were plotted.

Recovery of Injected Activity. Percent uptake of injected activity was summed for all operator-defined ROIs at 3 hr postdose administration, a time when blood-pool activity had substantially

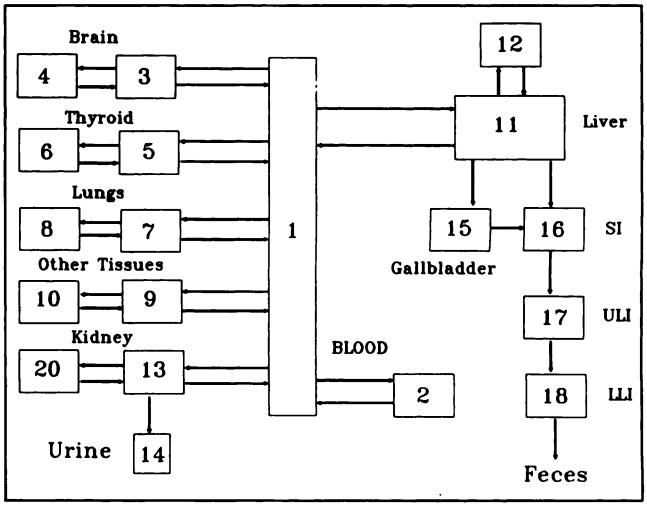

FIGURE 1. A multicompartmental model was used to describe the biodistribution and excretion of [^{123}I]iomazenil and estimate residence times for each subject. The model used a dynamic bladder submodel and a submodel of the ICRP 30 gastrointestinal tract model. SI is the small intestine and ULI and LLI are upper and lower large intestine, respectively.

cleared and before urinary or fecal elimination of tracer. Mean recovery of decay-corrected %ID at 3 hr from the summed ROIs was 114%. One possible reason for this overestimation is that the pad source of activity was not in a scattering medium, whereas emissions in the human subjects were scattered by the surrounding body tissues. ROIs did not overlap and therefore region drawing did not contribute to the error. When total activity in the whole-body images, including soft-tissue background, was measured and compared to the summed ROIs, recovery of administered activity was similarly overestimated. To correct for the measured recovery of administered activity, the time-activity data for each subject was normalized to 100% of the injected dose prior to dosimetry calculations.

Dosimetry Calculations. The time-activity curves for each organ were fitted using a multicompartmental model (Fig. 1) and SAAM (Simulation Analysis and Modeling) software (*14*). Most organs (brain, blood, thyroid, lungs, liver and kidneys) were treated as the sum of two compartments. The urinary bladder, gallbladder, small intestine, large intestine and remaining tissues were all treated as single compartments. Intercompartmental rate transfer coefficients (h^{-1}) for this model are denoted by L(x, y) where y is the source compartment/organ and x is the compartment/organ receiving the output from y.

The cumulative urinary excretion data fitted to the compartmental model were used to predict the urinary excretion rates and the fecal excretion fraction via hepatic clearance to the gastrointestinal tract. The model shown in Figure 1 illustrates the pathway from the central compartment to the kidneys [L(13,1)] and from the kidneys to the cumulative urinary bladder [L(14,13)]. Activity in the lower GI tract was assumed to be supplied by hepatobiliary clearance. Output of activity from the liver was divided between the gallbladder [L(15,11)] and small intestine [L(16,11)] with some activity returning to the central compartment [L(1,11)]. Of the material transferred through the biliary pathway, 30% was assumed to pass through the gallbladder and 70% was assumed to pass directly to the small intestine. In this model, the gallbladder cleared activity every 6 hr into the small intestine [L(16,15)] with

a rate transfer coefficient of 1.2 h^{-1} for 2 hr, then began to accumulate activity from the liver again for the next 4 hr. Material in the intestines was assumed to be transferred according to the kinetic model for the GI tract in ICRP 30 (*15*).

Residence times for the source organs were calculated by integration of the model-predicted activity retention in 11 organs or tissues: brain, thyroid, kidneys, liver, lungs, gallbladder, small intestine, upper large intestine, lower large intestine, urinary bladder contents and the remainder of the body. Remainder of the body residence time was estimated by integration of the activity predicted to be retained in compartments 1, 2, 9 and 10.

Absorbed doses for [^{123}I]iomazenil were calculated using MIRDOSE3 and utilizing the standard MIRD technique (*16*) for the adult male phantom (*17*). The urinary bladder was assumed to void once every 4.8 hr.

Iodine-125-Iomazenil Binding to Tissue Homogenates. To determine whether benzodiazepine receptors are present in human thyroid, radioligand binding with [^{125}I]iomazenil was performed to tissue homogenates prepared from postmortem human thyroid tissue following the methods of Johnson et al. (*8*). Thyroid tissue was obtained postmortem from two human subjects who had died without known endocrinological abnormalities. Tissue was stored at −70°C for 1–6 mo prior to use. Tissue was homogenized with a Polytron tissue grinder, setting 6 for 30 sec (Kinematica, Lucerne, Switzerland) at 20-fold dilution (weight:volume) in ice-cold 25 m*M* potassium phosphate buffer, pH 7.4, and the homogenates were centrifuged at 50,000 × g for 10 min at 4°C. Pellets were resuspended in 20 volumes buffer and centrifuged again; this process was repeated twice. The final resuspension was in 10 volumes incubation buffer (25 m*M* potassium phosphate, pH 7.4, containing 150 m*M* NaCl).

To triplicate incubation tubes were added: 400 μl resuspended tissue; 50 μl [^{125}I]iomazenil (for a final concentration of 10 p*M* radioligand of specific activity of approximately 2,000 Ci/mmole); and 50 μl buffer or nonradioactive iomazenil. Tubes were incubated at 21°C for 45 min. The assay was terminated by rapid filtration through GF/B glass fiber filters on a Brandel cell harvester (Biomedical Research & Development, Gaithersburg, MD) and washed with 3 × 5 ml ice-cold buffer. Radioactivity trapped in the filter was measured in an automated gamma counter. Specific binding was defined as the excess over nonspecific binding measured in the presence of 1 μ*M* clonazepam. Displacement with nonradioactive iomazenil was analyzed as a saturation isotherm using the "COLD" displacement option of the LIGAND program (Elsevier-Biosoft, Cambridge, U.K.).

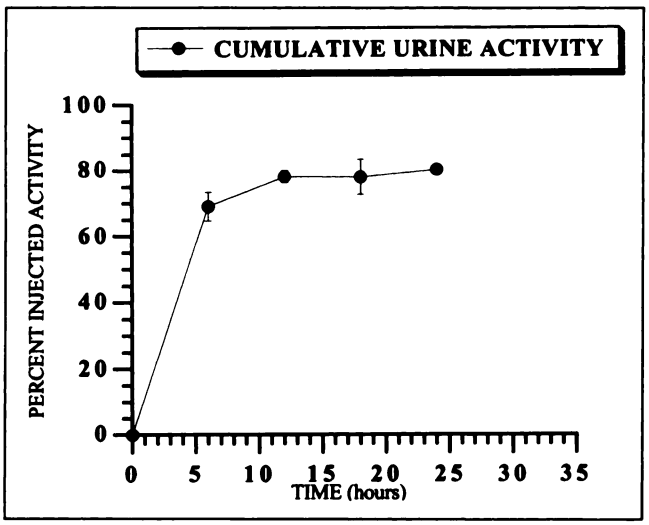

FIGURE 2. Urinary excretion data showed rapid early loss of activity. Displayed data are averaged over the seven subjects for whom fractionated urine samples were available at 6, 12 and 18 hr postinjection. Two of the subjects provided an additional urine collection at 24 hr. Standard error bars describe the range of activity present in cumulative urine samples at each time point.

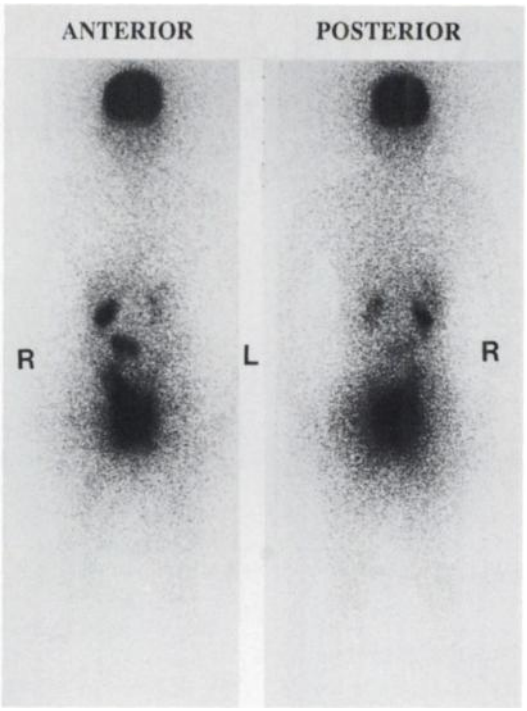

FIGURE 3. Whole-body images obtained from a healthy volunteer approximately 3 hr after [^{123}I]iomazenil injection. Scan acquisition time was 15 min. The anterior (A) and posterior (B) views show avid uptake in brain and demonstrate enterohepatic and urinary excretion of tracer.

RESULTS

Biodistribution of [^{123}I]Iomazenil

All eight subjects successfully completed the imaging protocol. Cumulative urinary excretion data were available for seven of the subjects and showed that approximately 78% of the administered activity was excreted within the first 24 hr after injection (Fig. 2). Of this 24 hr total, 88% was excreted within 6 hr of dose administration. Visual analysis of the acquired body scans showed avid brain uptake of the radiopharmaceutical (Fig. 3). A low level of body background activity was present at 3 hr postinjection. Activity noted within the bladder, gallbladder and bowel provided clear evidence of excretion through the renal and enterohepatic routes. No other major organ systems showed significant uptake of iomazenil by visual inspection of the scans, except for a small amount of activity noted within the thyroid bed in two subjects.

Analysis of organ-specific time-activity curves (Fig. 4) showed maximal brain uptake of [^{123}I]iomazenil at approxi-

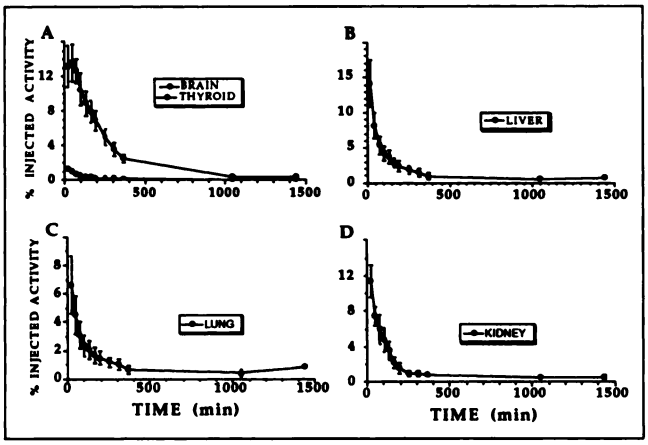

FIGURE 4. Time-activity curves were generated from organ-specific ROIs and fit to a multicompartmental model (Fig. 1) to describe tracer distribution and transfer. Data averaged over eight subjects are shown with standard error bars describing the range of activity noted within the group at each time point.

mately 30 min postinjection. Peak brain uptake in these healthy subjects was 13.7% ± 2.4% of the administered dose.

Dosimetry Estimates

Using the compartmental model depicted in Figure 1, residence times were calculated for 11 individual organs for each of the eight subjects (Table 1), and radiation absorbed doses were estimated for ^{123}I (Table 2).

The three organs receiving the largest absorbed doses were involved in excretion of iomazenil from the body: urinary bladder wall (0.19 mGy/MBq), lower large intestine wall (0.079 mGy/MBq) and upper large intestine wall (0.066 mGy/MBq). The thyroid received a relatively large absorbed dose also (0.063 mGy/MBq), and the absorbed dose to the brain was 0.018 mGy/MBq. The absorbed dose to the ovaries (0.02 mGy/MBq) was approximately four times higher than the absorbed dose to the testes (0.0053 mGy/MBq). The effective dose equivalent was estimated to range from 0.028 to 0.043 mSv/MBq. The total amount of activity predicted to be excreted in the feces was 10%–15%. The total amount of activity predicted to be excreted in the urine was approximately 85%–90%.

TABLE 1
Residence Times for [^{123}I]Iomazenil

Organ	Residence Time (hr)	1 s.d.
Brain	0.630	0.161
Thyroid	0.060	0.028
Lungs	0.285	0.174
Liver	0.467	0.137
Kidney	0.300	0.105
Urinary bladder (4.8-hr void)	2.456	0.245
Urinary bladder (2-hr void)	0.949	0.105
Gallbladder contents	0.163	0.065
Small intestine	0.529	0.215
Upper large intestine	1.022	0.415
Lower large intestine	0.835	0.339
Remainder of the body	0.748	0.421

TABLE 2
Radiation Dose Estimates for [^{123}I]Iomazenil

Organ	μGy/MBq	mrad/mCi	%COV*
Urinary bladder wall (4.8-hr void)	190	700	10
LLI wall	79	290	34
Urinary bladder wall (2-hr void)	74	270	9
ULI wall	66	240	36
Thyroid	63	230	46
Gallbladder wall	47	170	36
Kidneys	31	110	32
Small intestine	29	110	34
Uterus	23	85	4
Ovaries	20	74	23
Brain	18	67	26
Liver	12	44	23
Lungs	8	31	53
Bone surfaces	6	21	11
Testes	5	20	7
Red marrow	4	16	14
Adrenals	4	15	18
Stomach	4	16	20
Muscle	4	16	8
Pancreas	4	16	16
Spleen	3	12	19
Heart wall	2	8	25
Skin	2	6	13
Thymus	1	5	32
Breasts	1	4	30
Effective dose equivalent	33 μSv/MBq	120 mrem/mCi	12

*%COV = standard deviation of the absorbed dose for each organ expressed as a percentage of the mean absorbed dose.

Radioligand Binding to Thyroid Tissue

Thyroid activity was presumed to result from deiodination of the ligand and uptake of [^{123}I]iodide. Alternatively, this activity may have represented binding of [^{123}I]iomazenil to benzodiazepine receptors.

Radioligand binding studies were performed with [^{125}I]-iomazenil to homogenates prepared from human thyroid and cerebellar tissue. Displacement with nonradioactive iomazenil was analyzed as a saturation isotherm. The displacement studies revealed a B_{max} (number of binding sites) of 0.11 ± 0.02 fmole/mg wet weight and a K_D (dissociation constant) of 1.4 ± 0.1 n*M* (mean + s.e.m., n = 3 for both B_{max} and K_D). These values may be compared to those of human cerebellar tissue which were concurrently measured in the same binding assay as the thyroid tissue and showed B_{max} of 32.9 ± 10.4 fmole/mg original wet weight and a K_D of 0.5 ± 0.2 n*M*, values that are similar to previous results (*8*). These binding experiments demonstrated saturable, high affinity benzodiazepine radioligand binding to human thyroid tissue which has approximately 300 times fewer binding sites per milligram tissue than human cerebellum.

DISCUSSION

The biodistribution of [^{123}I]iomazenil has been previously described in animals (*5,6,11*). In the rat, peak brain uptake was achieved at 10 min postinjection and represented 3.2% of the administered activity/g. Activity in liver and kidney also peaked at 10 min and showed the highest organ accumulations of radioactivity, corresponding to 5.6% and 7.1% of administered activity/g, respectively. After 1 hr, almost all activity was cleared from the blood pool, while the brain retained significant activity levels.

Similarly, whole-body distribution of iomazenil in humans has been reported to parallel that in animals. Studies in healthy volunteers (*6*) at 2 and 90 min postinjection have shown high initial uptake in the brain, with excretion through the kidneys and in the bile. No significant uptake in other organs was identified. The results of the current study confirm these findings and extend them by examining later time points.

Dosimetry estimates for [^{123}I]iomazenil have been previously published based on extrapolation from animal data (*6*). The estimates presented here, based on human biodistribution data, generally show a 2–3-fold higher absorbed dose per organ than those inferred from animal data, although the estimates remain well within the range of doses acceptable in clinical nuclear medicine studies.

Most recently, Verhoeff et al. (*18*) described dose estimates for [^{123}I]iomazenil derived from whole-body scans performed on healthy adult volunteers. A comparison of Verhoeff's study and our own reveal significant methodologic differences. Verhoeff et al. acquired data at only two time points, 1 and 3 hr postinjection and fit a monoexponential curve to the two data points. Data were acquired from our subjects at 12 separate time points from 30 min to 24 hr after tracer administration and the resulting time-activity curves were fitted using a multicompartmental model. We corrected the whole-body images for regionally variable organ attenuation using a transmission scan. Verhoeff et al. did not.

The use of more time points and regionally variable attenuation factors would be expected to increase the accuracy of the dose estimates. Surprisingly, the radiation dose estimates derived by Verhoeff et al. are quite similar to our own, with an identical effective dose equivalent. The high correlation between the dose estimates from our two groups may derive from the fact that [^{123}I]iomazenil is primarily (85%–90%) excreted through the urine. Verhoeff et al. assumed that all activity was excreted in the urine. Our later images, however, clearly demonstrate excretion through the enterohepatic route and presumably underlie our almost twofold higher dose estimates for gastrointestinal tract organs (gallbladder, liver, small and large intestine). If an even greater percentage of activity had been excreted through the bowel, then larger discrepancies and presumed inaccuracies would result from the use of images acquired at only two time points.

Based on almost 90% urinary excretion of activity and assuming a 4.8-hr void, we calculated the absorbed dose to the urinary bladder wall to be 0.19 mGy/MBq. Significant reduction in the urinary bladder dose could be achieved by encouraging frequent voiding during the first several hours after radioligand injection. An optimal bladder voiding schedule can be determined from MIRD Dose Estimate Report 14 (*19*).

Despite thyroid blockade with Lugol's solution, some of our subjects showed significant accumulation of tracer within the thyroid bed. This finding was surprising in view of the amount of stable iodide administered prior to injection. Acute protection of the thyroid gland can be achieved with the administration of approximately 0.3 ml of Lugol's solution for 1 to 2 days prior to exposure (*20*). Our subjects received 0.3 to 0.5 ml the day prior to and again on the day of exposure, yet up to 1.8% of injected radioactivity was detected in the thyroid. The unblocked radioactivity could be attributed in part to the presence of benzodiazepine radioligand binding sites on human thyroid tissue. In vitro binding measurements showed saturable, high affinity binding to thyroid tissue, which had 300-fold lower number of sites than human cerebellum. As part of a related animal study, we extracted activity from the tissues of monkeys which were euthanized 2 hr postinjection of [^{123}I]iomazenil. Although data from the thyroid were not previously reported, we found that 16% of the total radioactivity present in the thyroid of this animal was parent compound (*11*). These data are consistent with thyroid uptake of parent compound that may bind to benzodiazepine receptors in this organ. Furthermore, these data suggest that additional doses of stable iodide would not decrease the portion of thyroid uptake representing benzodiazepine radioligand binding.

In summary, the biodistribution of [^{123}I]iomazenil in eight healthy human subjects demonstrated high and stable brain uptake with whole-body dosimetry favorable for clinical SPECT imaging.

ACKNOWLEDGMENTS

The authors thank Gary Wisniewski for assistance with the whole-body images; Suzanne Giddings for the binding studies; Leo Kelly (Pathology Service, West Haven VA Medical Center) for obtaining thyroid tissue; and Dr. Walter Hunkeler (Hoffmann-La Roche, Basel, Switzerland) for providing nonradioactive iomazenil. This work was supported in part by funds from the VA National Center for Post-traumatic Stress Disorder, a VA Merit Review Award to RBI and a VA Research Advisory Group Award to HMD. This work was performed in part under Interagency Agreement no. FDA 224-75-3016, DOE 40-286-71. Oak Ridge Associated Universities performs complementary work for the U.S. Department of Energy under contract DE-AC05-76OR00033. Ms. Olson is a fellow in the Applied Physics Program administered by ORISE for the DOE.

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