

Quantitation of benzodiazepine receptor binding with PET [¹¹C]iomazenil and SPECT [¹²³I]iomazenil: preliminary results of a direct comparison in healthy human subjects

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Abstract

Although positron emission tomography (PET) and single photon emission computed tomography (SPECT) are increasingly used for quantitation of neuroreceptor binding, almost no studies to date have involved a direct comparison of the two. One study found a high level of agreement between the two techniques, although there was a systematic 30% increase in measures of benzodiazepine receptor binding in SPECT compared with PET. The purpose of the current study was to directly compare quantitation of benzodiazepine receptor binding in the same human subjects using PET and SPECT with high specific activity [¹¹C]iomazenil and [¹²³I]iomazenil, respectively. All subjects were administered a single bolus of high specific activity iomazenil labeled with ¹¹C or ¹²³I followed by dynamic PET or SPECT imaging of the brain. Arterial blood samples were obtained for measurement of metabolite-corrected radioligand in plasma. Compartmental modeling was used to fit values for kinetic rate constants of transfer of radioligand between plasma and brain compartments. These values were used for calculation of binding potential ($BP = B_{\max}/K_d$) and product of BP and the fraction of free non-protein-bound parent compound ($V3'$). Mean values for $V3'$ in PET and SPECT were as follows: temporal cortex 23 ± 5 and 22 ± 3 ml/g, frontal cortex

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23 ± 6 and 22 ± 3 ml/g, occipital cortex 28 ± 3 and 31 ± 5 ml/g, and striatum 4 ± 4 and 7 ± 4 ml/g. These preliminary findings indicate that PET and SPECT provide comparable results in quantitation of neuroreceptor binding in the human brain. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Positron emission tomography; Single photon emission computed tomography; Benzodiazepine receptor binding; Compartmental modeling; Kinetic rate constants; Methodology

1. Introduction

The assessment of benzodiazepine receptors in living human brain is relevant to the study of several neuropsychiatric and neurological disorders (Pike et al., 1993). These techniques, however, need to be validated by model-based methods of quantitation, since they have the potential to introduce confounds in the assessment of neuroreceptor binding. For instance, differences in peripheral clearance of radioligand between groups of patients and control subjects could lead to results that are not an accurate reflection of true differences in central benzodiazepine receptor binding. Also, differences in uptake in comparison with brain regions of low specific binding between groups may influence the outcome measures.

Techniques developed for quantitation of neuroreceptor binding (Huang and Phelps, 1986; Carson, 1991) have been applied to benzodiazepine receptor binding imaging with both positron emission tomography (PET) and single photon emission computed tomography (SPECT). Studies used PET and [^{11}C]flumazenil (Ro 15–1788) in the quantitation of benzodiazepine binding potential (BP) [equal to the ratio of receptor number (B_{max}) and affinity (K_{D})] (Koeppel et al., 1991; Abadie et al., 1992) as well as separate measurements of receptor number (B_{max}) and affinity (K_{D}) (Price et al., 1993).

Although PET was initially felt to represent the only viable method for quantitation of benzodiazepine receptor binding, more recently reliable and valid methods have been developed for quantitation of benzodiazepine receptor binding in human brain with SPECT using the benzodiazepine receptor antagonist [^{123}I]iomazenil (Ro 16-0154) (Beers et al., 1990; Innis et al., 1991; Sybirska et al., 1993; Laruelle et al., 1994; Abi-

Dargham et al., 1994, 1995). There are a number of differences, however, between PET and SPECT (reviewed below) which could influence quantitation of neuroreceptor binding. Given these differences, it is surprising that there has been only one direct comparison of PET and SPECT to date using any type of neuroreceptor ligand (Westera et al., 1996).

Iomazenil has been successfully labeled with both ^{11}C and ^{123}I for imaging with PET and SPECT (Beers et al., 1990; Zoghbi et al., 1992; Westera et al., 1993, 1996; Baldwin et al., 1995; Buck et al., 1996). Whether labeled with ^{11}C or ^{123}I , iomazenil has the same chemical formula but different isotopic substitutions of two of its constituent atoms. Iomazenil is therefore an ideal ligand for direct comparisons of quantitation with these two radiotracer methodologies. One study to date has directly compared PET and SPECT quantitation of the benzodiazepine receptor with iomazenil. Values for volume of distribution (V_{D}) measured with SPECT were higher than measures obtained with PET in the same subjects, although there was a high degree of correlation between the two measures (Westera et al., 1996). Use of low specific activity radioligand may explain differences in absolute values in this study. The purpose of the present study was to compare PET and SPECT using high specific activity radiolabelled iomazenil and arterial sampling in a direct comparison in the same healthy human subjects.

2. Methods

2.1. Subjects

The subjects comprised three healthy males without current or past histories of medical or

psychiatric illness as determined in the Structured Clinical Interview for DSM-III-R/non-patient version (Spitzer et al., 1987). Subjects had been free of all medications and alcohol for at least 4 weeks before the study and had no lifetime history of benzodiazepine use. All subjects were white and right-handed; their mean age was 26 years (S.D. = 3). All subjects underwent PET and SPECT imaging for quantitation of benzodiazepine receptor binding within a 4-week period. Subjects received potassium iodide (SSKI solution 0.6 g) in the 24-h period before the SPECT scan.

Subjects provided written informed consent. The protocol was approved by the local human investigation committee, and the research was performed in accordance with the Helsinki Act of 1964.

2.2. PET procedures

2.2.1. PET radiolabeling

For PET imaging, [*N*-methyl-¹¹C]iomazenil (Ro 16–0154) was synthesized by alkylation of the desmethyl precursor noriomazenil with [¹¹C]-methyl iodide. The [¹¹C]CH₃I was reacted with noriomazenil in *N,N*-dimethylformamide and Bu₄N⁺OH⁻ for 1 min at 80°C and purified by high performance liquid chromatography. The product was obtained with a radiochemical yield > 98% and specific activity = 100–500 Ci/mmol. These methods have been described in greater detail in a previous publication (Baldwin et al., 1995).

2.2.2. PET imaging methods

At the beginning of the PET imaging session, subjects were placed in a Posicam camera (Positron Corporation) with an intravenous and intra-arterial line in place. The Posicam is a 21-slice camera with a 5.125-mm interslice distance (Mulaney et al., 1990). Resolution determined as the value of full width at half maximum (FWHM) of a reconstructed image of a point source of radioactivity in water is 6 mm in-plane and 13 mm in the *z* axis. Subjects were positioned in the camera with head immobilized by a deformable mask and the canthomeatal line parallel to an external laser light. Four fiducial markers con-

taining 1–2 μCi ¹⁸F were attached on both sides of the subject's head at the level of the canthomeatal line to identify this plane during image analysis. Subjects rested with eyes open in a dimly lit room. Initially a transmission scan was performed with a rotating ⁶⁷Ga/⁶⁸Ge rod source for measurement of attenuation due to overlying bone and soft tissue. Subjects were next administered 14 mCi of high specific activity (100–500 Ci/mmol) [¹¹C]iomazenil in a single i.v. bolus over 30 s followed by PET imaging in list mode for 105 min. Arterial samples were obtained every minute for the first 4 min after injection with a peristaltic pump (Harvard 2501–001, South-Natick, MA, USA), and then manually at 6, 8, 12, 16, 20, 30, 45, 60, 75, 90, and 105 min after injection.

2.2.3. PET image reconstruction and analysis

PET list mode data were broken into images of 30-s duration for the first 2 min, then of 2.5-min duration for the next 18 min, and finally of 5-min duration for the rest of the period of acquisition. Images were reconstructed using RAMP and Butterworth filter on a 128 × 128 × 21 matrix (pixel size 1.9 × 1.9 mm, slice thickness = 5.125 mm). Images were inspected for movement during the imaging session by visualization of location of fiducial markers, and images were manually re-aligned to correct for motion artifact if necessary. Irregular regions of interest (ROIs) were drawn over left and right temporal cortex, frontal cortex, occipital cortex, and striatum, in three slices at the level of the striatum. An operator with training and experience in image interpretation (JDB) placed ROIs over areas of maximum radioligand uptake (indicating the presence of cortical activity). The mean levels of activity in the three slices and left and right ROIs were determined for generation of the final tissue activity curve for each ROI (frontal, temporal, occipital cortex and striatum). A 12-cm cylindrical fluid-filled phantom with a known amount of ¹⁸F was scanned for the determination of a calibration factor for conversion of radioactivity in the PET images (cpm) into absolute units of radioactivity (μCi).

2.3. SPECT procedures

2.3.1. SPECT radiolabeling

Subjects underwent a SPECT scan within 4 weeks of the PET scan. Carrier added [^{123}I]-iomazenil was prepared by iododestannylation of ethyl 7-(tributylstannyl)-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazol[1,5-*a*][1,4]benzodiazepine-3-carboxylate with chloramine-T in methanolic acetic acid at 120°C as previously described (Zea-Ponce et al., 1994). Carrier was added to achieve a specific activity of 100–500 Ci/mmol to be similar to that of the radioligand used in the PET experiments.

2.3.2. SPECT imaging methods

Subjects were placed in the Ceraspect (Digital Scintigraphics, Waltham, MA, USA) device with head positioned along the canthomeatal line and immobilized with head and chin straps. The Ceraspect is a 64-slice camera with a 1.5-mm interslice distance. Resolution was determined as the value of FWHM of a reconstructed image of a point source of radioactivity in water and was 1.3 cm. Four fiducial markers containing 10 μCi [$^{99\text{m}}\text{Tc}$]NaTcO₄ were attached on both sides of the subject's head at the level of the canthomeatal line to identify the canthomeatal plane during image analysis. Subjects rested with eyes open in a dimly lit room during the testing period. [^{123}I]iomazenil (6 mCi) were administered as a single i.v. bolus over 30 s followed by SPECT imaging of the brain for 130 min after injection. Images of 2-min duration were obtained for the first 10 images, and then images of 4-min duration were obtained until the end of the imaging session. Arterial samples were obtained every 20 s for the first 2 min after injection with a peristaltic pump (Harvard 2501–001, South Natick, MA, USA), and then manually at 3, 4, 6, 8, 12, 16, 20, 25, 30, 35, 45, 60, 90, and 120 min after injection.

2.3.3. SPECT image reconstruction and analysis

SPECT images were reconstructed from counts acquired in the ^{123}I photopeak (159 keV) with a 20% symmetric window using RAMP and Butterworth filter (cutoff = 1 cm, power factor = 10) on a 64 × 64 × 64 matrix (pixel size = 3.3 × 3.3 mm,

slice thickness = 1.15 mm, voxel volume = 16.2 mm³). Adjacent slices were then summed to obtain a 32-slice image with an interslice distance of 3.3 mm. Uniform attenuation correction ($\mu = 0.15 \text{ cm}^{-1}$) was performed based on an ellipse placed over the skin surface as identified by fiducial markers (Chang, 1978). Images were inspected for movement during the imaging session by visualization of location of fiducial markers and were manually realigned to correct for motion artifact if necessary. Irregular uniform ROIs of equivalent size to those used for PET image analysis were placed over left and right temporal cortex, frontal cortex, occipital cortex, and striatum, in five slices at the level of the striatum. Five slices were selected to be equivalent to the distribution of sampling of images in the *z*-axis in the PET images described above. The interslice distance was less for SPECT (3.3 mm) than for PET (5.125 mm). An operator with training and experience in image interpretation who also placed ROIs on the PET images (J.D.B.) placed ROIs over areas of maximum radioligand uptake (indicating the presence of cortical activity). Mean levels of activity in the five slices and left and right ROIs were determined for generation of the final tissue-activity curves (frontal, temporal, occipital cortex and striatum). A 12-cm cylindrical fluid-filled phantom with a known amount of ^{123}I was scanned for the determination of a calibration factor for conversion of radioactivity in the SPECT images (cpm) into absolute units of radioactivity (μCi).

2.4. PET and SPECT arterial plasma analysis

Plasma was separated by centrifugation and analyzed for concentration of radioligand and metabolites in plasma using methods previously described (Zoghbi et al., 1992). Extraction (ethyl acetate) was followed by reverse-phase high performance liquid chromatography to measure the metabolite-corrected total plasma activity in units of microcuries per milliliter. Measured metabolite-corrected total plasma activity data were fit to a sum of three exponentials, and values for the zero time intercepts and λ elimination rate constants (min^{-1}) of the three exponen-

tials were determined. Initial volume of distribution was calculated as the injected dose divided by the sum of the zero time intercepts.

The free fraction of plasma parent compound (f_1 = free parent/metabolite-corrected total plasma activity) was measured in each subject by ultrafiltration with the Centrifree micropartition system using methods previously described (Gandelman et al., 1994).

2.5. Data analysis and kinetic modeling for PET and SPECT

Time–activity curves were generated for concentration of radioligand in brain and concentration of total parent compound in plasma at multiple time points after administration of radioligand for both PET and SPECT studies. The data were analyzed using two- and three-compartment models. In the three-compartment model, V_2 is volume of distribution of free and non-specifically bound radioligand in the brain, and V_3 is the volume of distribution of radioligand specifically bound to receptor in the brain (which is equal to the binding potential, BP). The BP in the three-compartment model is equal to $K_1 \times K_3/k_2 \times k_4 \times f_1$, where K_1 represents rate of transfer from blood to brain; k_2 , rate of transfer from brain to blood; k_3 , rate of transfer from non-specific or unbound to specifically bound radioligand; k_4 , rate of transfer from specifically bound to nonspecifically bound; and f_1 is the fraction of parent compound in plasma that is non-protein bound and available for uptake into the brain. V_2 in the three-compartment model is equal to $K_1/(k_2 \times f_1)$. In the two-compartment model, volume of distribution (V_T), is equal to $V_2 + V_3$, or K_1/k_2 . Assuming non-specific binding to be negligible (which is reasonable considering the very high ratio of specific to non-specific binding of this radioligand), V_T is equivalent to the binding potential. By this formulation, V_T and V_3 are expressed relative to the free fraction of tracer in plasma. When expressed relative to total plasma tracer, these values are designated V_T' and V_3' and have equivalent formulae with the elimination of the f_1 value. V_T' and V_3' have been shown

to have a higher level of reliability than V_T and V_3 (Abi-Dargham et al., 1995).

Compartmental modeling was performed with the Statistical Analysis and Modeling-II (SAAMII) program (Seattle, WA, USA). Values for K_1 – k_4 were determined by fitting the models to the time–activity curves for the various ROIs and fitted curves of total parent compound in plasma as the input function, and minimizing sum of squares of the residuals. Constraining the value of V_2 in the three-compartment model has been shown to increase the accuracy and reproducibility of the binding potential measurement (Laruelle et al., 1994). The value of V_2 was therefore constrained at 3.2. The constraint was based on results in humans using receptor-saturating doses of flumazenil (0.2 mg/kg) in bolus plus constant infusion experiments to determine the non-displaceable compartment (Abi-Dargham et al., 1994). In these experiments there were no significant differences between regions in the non-specific volume of distribution. Therefore, the same constraint was used for all regions. Unconstrained two-compartment modeling was also performed. Values of kinetic rate constants were used in the determination of binding potential and other measures of volume of distribution.

3. Results

3.1. PET and SPECT imaging

Radioligand distributed throughout cortical regions, with lesser uptake in striatum, and essentially no uptake in white matter regions for both PET and SPECT experiments. Representative images for PET and SPECT (see Fig. 1) show superior resolution for PET in comparison to SPECT. Fig. 2 Shows activity in brain for temporal, frontal, and occipital cortex and striatum in a representative subject for PET and SPECT. There were similar time–activity curves for PET and SPECT.

3.2. Arterial plasma analysis

Fig. 3 presents total radioactivity and unmetabolized non-protein-bound total parent compound

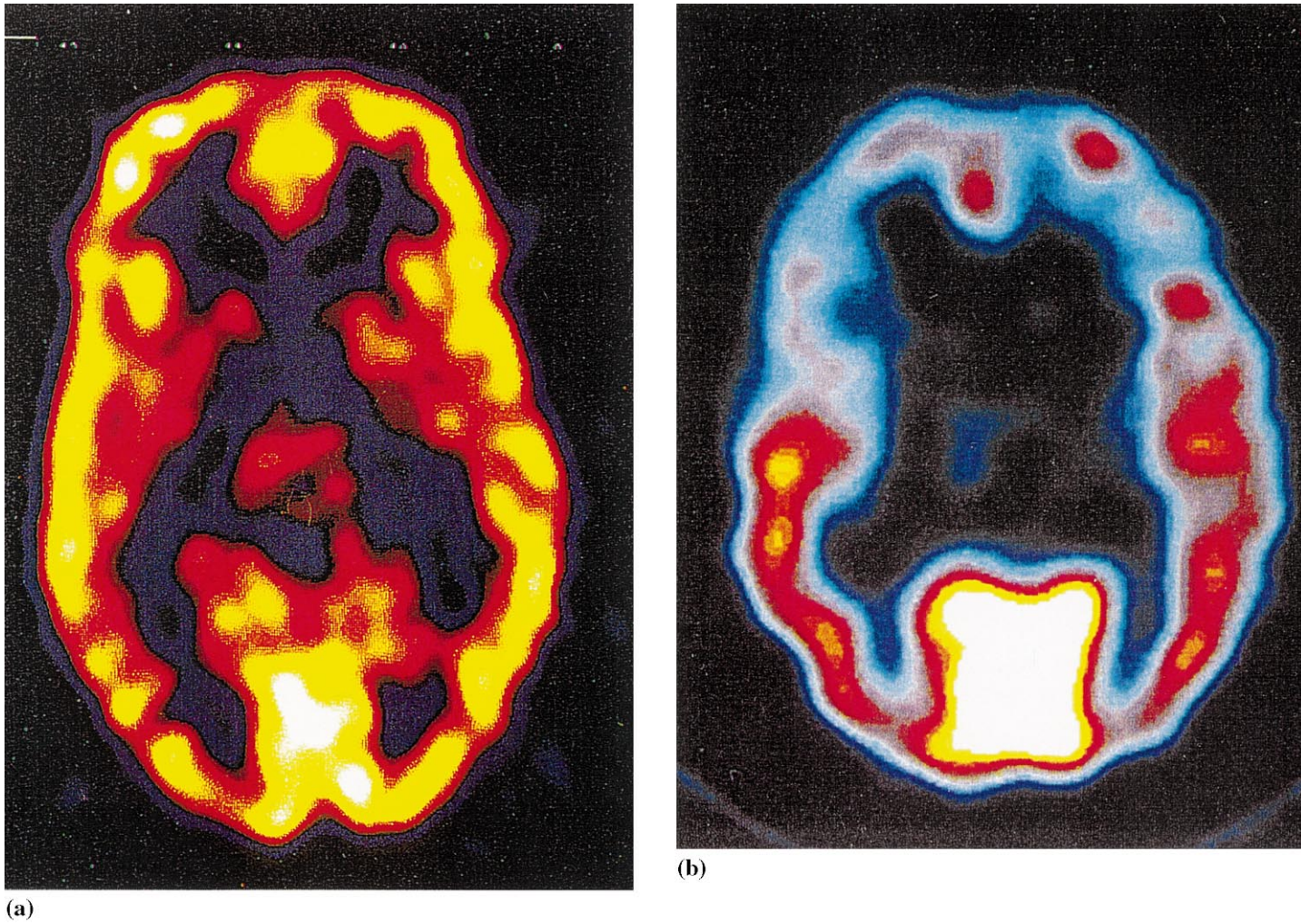


Fig. 1. Axial images of radioligand distribution for PET [^{11}C]iomazenil (a) and SPECT [^{123}I]iomazenil (b) in a healthy human subject. Better resolution is visually appreciable in the PET vs. SPECT scan.

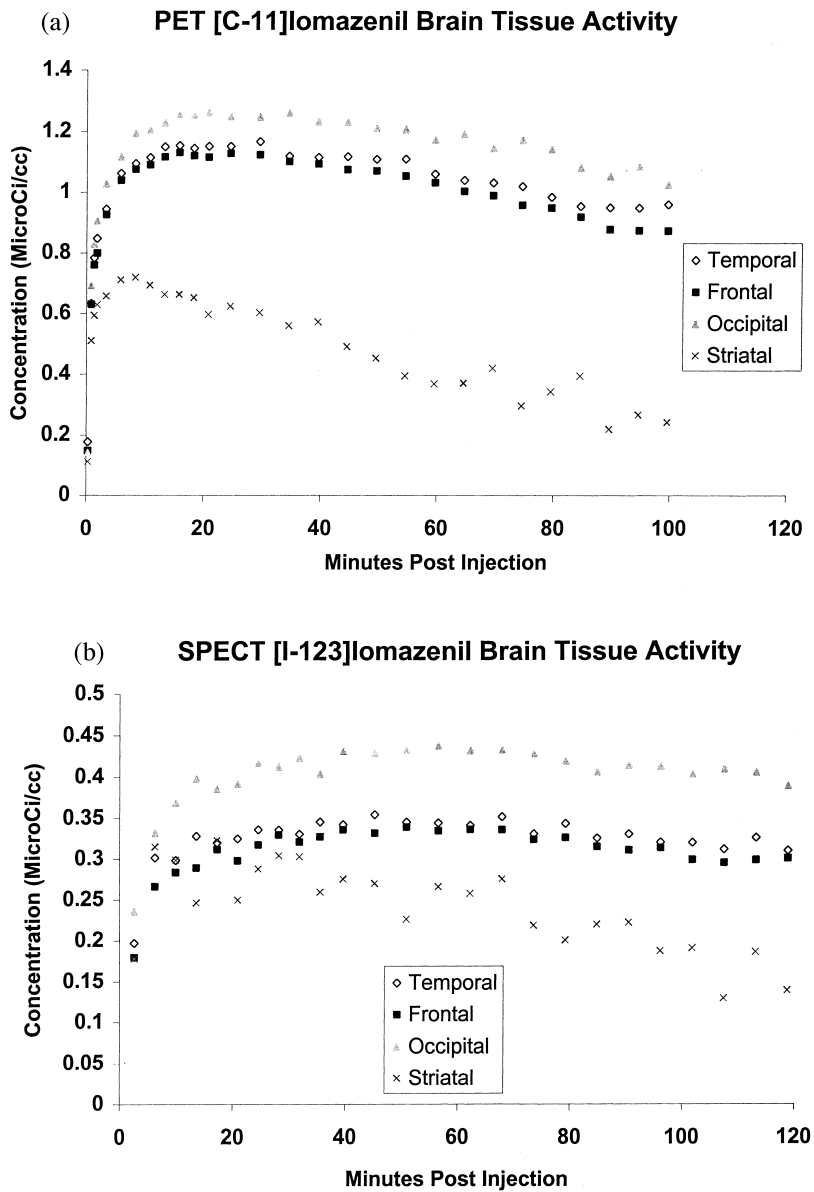


Fig. 2. Concentration of radioactivity ($\mu\text{Ci}/\text{cm}^3$) in temporal, frontal, occipital cortical and striatal regions of brain following injection of radioligand for experiments using PET [^{11}C]iomazenil (a) and SPECT [^{123}I]iomazenil (b) in a representative healthy human subject. Similar time–activity curves were seen for PET and SPECT in the same subject.

concentrations in arterial plasma after injection in a representative subject for PET and SPECT studies. Consistent with previous studies (Westera et al., 1996), there was rapid metabolism and

clearance of radioligand from plasma in both the PET and SPECT experiments, with more than 80% of parent compound removed within the first 10 min.

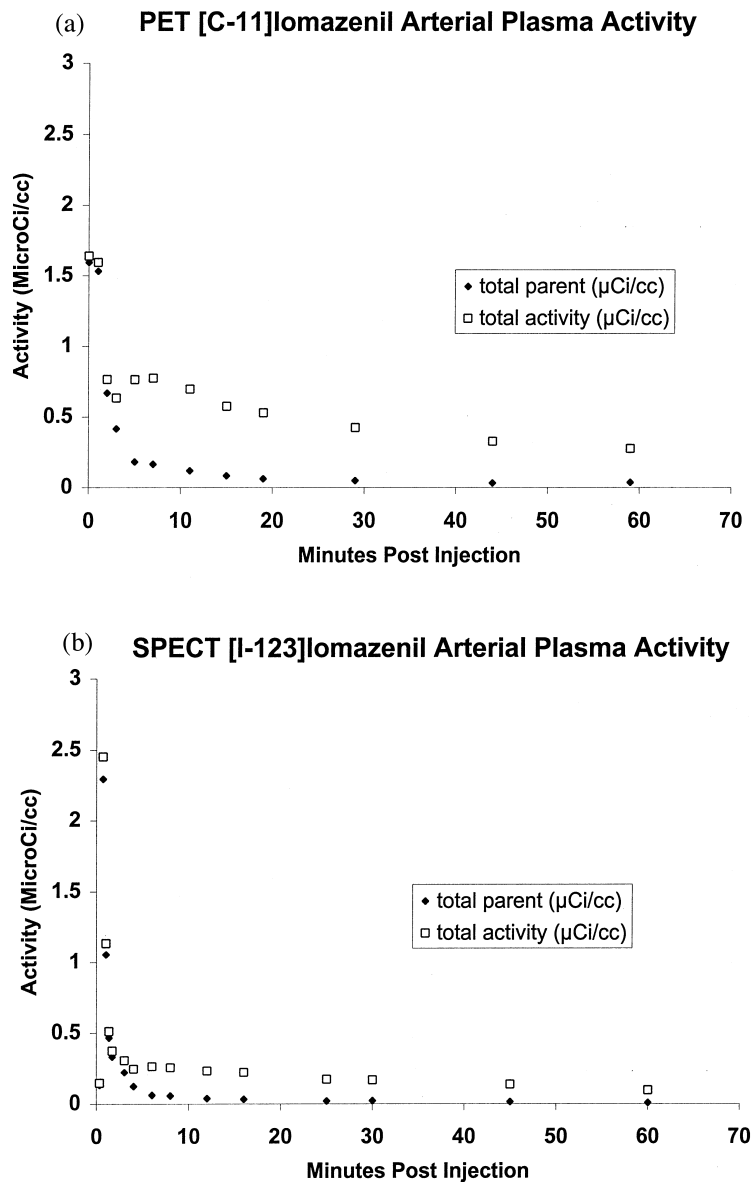


Fig. 3. Concentration of radioactivity ($\mu\text{Ci}/\text{cm}^3$) in arterial plasma of total radioactivity and unmetabolized total non-protein-bound iomazenil following injection of PET [^{11}C]iomazenil (a) and SPECT [^{123}I]iomazenil (b) in a representative healthy human subject. There was rapid metabolism and clearance of radioligand from plasma for both experiments.

3.3. PET and SPECT data analysis

Tables 1 and 2 present values for kinetic rate constants and measures of benzodiazepine recep-

tor binding for the two-compartment model and the three-compartment, respectively. There were lower residual sum of squares after the fits for the three-compartment model in comparison to the two-compartment model, consistent with previous

Table 1

Mean values and S.D. for kinetic rate constants and measures of receptor binding in PET and SPECT based on kinetic modeling with a two-compartment model

		K_1	S.D.	k_2	S.D.	V_T	S.D.	V_T	S.D.	AIC	S.D.
Temporal	PET	0.204	0.041	0.012	0.001	48.1	5.5	17.4	1.7	2.38	0.32
	SPECT	0.166	0.085	0.008	0.004	68.1	6.1	21.3	2.7	0.94	1.19
Frontal	PET	0.223	0.058	0.012	0.000	51.1	14.5	18.4	4.8	2.37	0.36
	SPECT	0.152	0.075	0.008	0.005	66.1	23.0	20.8	8.1	0.98	1.14
Occipital	PET	0.243	0.050	0.011	0.001	59.3	11.4	21.4	3.6	2.12	0.74
	SPECT	0.197	0.085	0.006	0.003	101.1	12.2	31.5	4.7	0.83	1.13
Striatum	PET	0.178	0.035	0.030	0.008	17.9	8.0	6.4	2.8	2.15	0.01
	SPECT	0.125	0.042	0.017	0.008	27.0	11.0	8.5	3.7	1.23	0.89

studies (Laruelle et al., 1994). Overall there were similar values for measures of benzodiazepine receptor binding, measured with the binding potential (V_3) and the related measure V_3' (product of binding potential and the fraction of non-protein-bound plasma parent compound $-f_1$) for the three-compartment model. Values for V_3' were similar within the same subjects as determined by PET and SPECT techniques. Mean values for V_3' in PET and SPECT, respectively, were as follows: temporal cortex, 23 ± 5 and 22 ± 3 ml/g; frontal cortex, 23 ± 6 and 22 ± 3 ml/g; occipital cortex, 28 ± 3 and 31 ± 5 ml/g; and striatum, 4 ± 4 and 7 ± 4 ml/g (with these and subsequent values expressed as mean \pm S.D.). The percent differences between PET and SPECT measures of V_3' (calculated as $\text{PET } V_3' - \text{SPECT } V_3' / \text{SPECT } V_3'$) were as follows: temporal cortex, $+3 \pm 13$; frontal cortex, $+12 \pm 45$; occipital cortex, -11 ± 15 ; striatum, $+29 \pm 180$. Table 2 presents values for BP and other measures of benzodiazepine binding. Goodness of fit, as determined by the Akaike Information Criteria (AIC), was lower in the three-compartment model than in the two-compartment model for both PET and SPECT, indicating a better fit to the data with the three-compartment model. The AIC also tended to be lower for SPECT than PET. There was a significant correlation between values for V_T' as determined by PET and SPECT across subjects and ROIs ($r = 0.87$, d.f. = 11, $P < 0.05$) (Fig. 4). Correlations were also seen within individual brain regions for temporal cortex ($r = 0.77$) and frontal cortex ($r =$

0.60), with weaker correlation for occipital cortex ($r = 0.24$) and no correlation for striatum.

4. Discussion

PET and SPECT measurements of benzodiazepine receptor binding with iomazenil yielded similar results in direct comparisons in the same human subjects. Mean percent differences between PET and SPECT in quantitation of benzodiazepine neuroreceptor binding ranged from 2 to 12% for cortical regions with high specific binding. These results are similar to previous findings of an approximately 10% difference between test and retest in quantitation of benzodiazepine receptor binding using SPECT (Abi-Dargham et al., 1994). The results support the idea that methods for quantitation of neuroreceptor binding used in PET and SPECT studies provide valid estimates of neuroreceptor binding.

Only one other study directly compared neuroreceptor quantitation with PET and SPECT in the same human subjects (Westera et al., 1996). That study found a high correlation between values for benzodiazepine receptor binding obtained with PET and SPECT. Values for SPECT were systematically higher than corresponding values for PET, however, with mean values for distribution volume (DV) derived from 90 min of imaging data with each modality being 21% higher in occipital cortex, 16% higher in frontal cortex, and 7% higher in temporal cortex (Westera et al.,

Table 2

Mean values and S.D. for kinetic rate constants and measures of receptor binding in PET and SPECT based on kinetic modeling with a three-compartment model

Region	Modality	K_1 ml g ⁻¹ min ⁻¹	S.D.	k_2 min ⁻¹	S.D.	k_3 min ⁻¹	S.D.	k_4 min ⁻¹	S.D.	V_3 ml g ⁻¹	S.D.	V_3' ml g ⁻¹	S.D.	V_T ml g ⁻¹	S.D.	V_T' ml g ⁻¹	S.D.	AIC	S.D.	
Temporal	PET	0.353	0.088	0.11	0	0.028	0.104	0.021	0.015	0.004	62.2	14.0	22.5	4.7	71.1	14.0	25.9	5.0	1.67	0.35
	SPECT	0.288	0.180	0.09	0	0.056	0.241	0.131	0.037	0.022	70.9	7.9	21.5	2.8	81.5	7.7	24.7	2.8	0.59	0.13
Frontal	PET	0.346	0.107	0.10	8	0.034	0.088	0.028	0.012	0.003	64.2	16.5	23.2	5.5	73.2	16.5	26.4	5.5	1.62	0.32
	SPECT	0.276	0.186	0.08	6	0.058	0.243	0.136	0.037	0.022	71.3	9.7	21.6	3.3	81.9	9.6	24.8	3.3	0.71	0.15
Occipital	PET	0.392	0.105	0.12	2	0.033	0.098	0.019	0.011	0.001	76.9	9.1	27.6	3.0	85.8	9.1	31.0	2.6	1.69	0.39
	SPECT	0.309	0.135	0.09	7	0.041	0.395	0.218	0.039	0.019	103.5	17.2	31.3	4.7	114.0	17.4	34.5	4.7	0.39	0.08
Striatum	PET	0.247	0.093	0.07	7	0.029	0.032	0.021	0.035	0.015	11.0	9.9	3.9	3.5	19.8	10.1	7.1	3.5	1.45	0.41
	SPECT	0.190	0.061	0.05	9	0.019	0.101	0.074	0.041	0.015	22.9	13.8	6.9	4.1	33.4	14.1	10.1	4.1	0.74	0.37

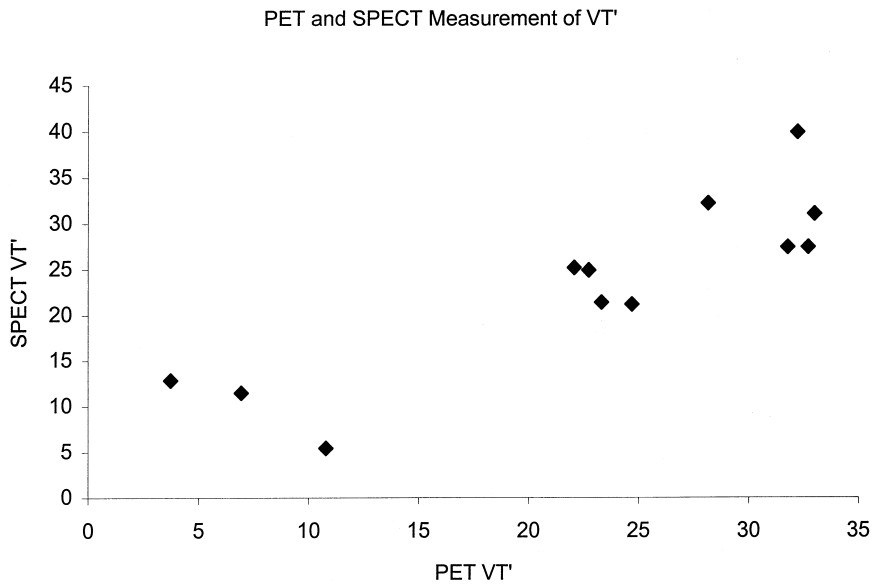


Fig. 4. Relationship between outcome measures of benzodiazepine receptor binding (V_T') measured with PET and SPECT. Individual symbols correspond to values of V_T' measured with PET and SPECT in different brain regions across subjects.

1996). One possible explanation for these findings may be related to the fact that this study used relatively lower specific activity radioligand (4–25 Ci/mmol) than was used in the current study (100–500 Ci/mmol). High specific activity radioligand is required to maintain negligible receptor occupancy, without which the radioligand competes for binding sites with endogenous ligand, influencing quantitative assessment of receptor number. Secondly, venous samples were used for determination of parent compounds in plasma in the SPECT (but not the PET) experiments. Different quantitative results are obtained for determination of [^{123}I]iomazenil parent compound when venous samples are used as opposed to arterial samples (Zoghbi et al., 1992). In the prior study an extrapolation from PET data (in which arterial samples were obtained) to SPECT data was performed within the same subjects in an attempt to correct for this discrepancy. Both the earlier study (Westera et al., 1996) and the current one assume that the uptake, distribution and metabolism of [^{123}I]iomazenil and [^{11}C]iomazenil are identical. There may be differences in the characteristics of these two compounds or their

radiolabelled metabolites that influence availability for uptake into the brain that would be missed by this approach.

In the current study there was a pattern of better fit in compartmental modeling using SPECT data in comparison to PET data as assessed with the Akaike Information Criteria (AIC). Although the SPECT data were acquired for a longer period of time after injection of radioligand (130 min in SPECT vs. 105 min in PET), the better fit for the SPECT data held true even when the modeling was restricted to an equal time period for both studies. This may be related to the reduced noise in later data points for both the plasma and brain radioligand concentration data in SPECT vs. PET, due to the longer half-life of ^{123}I compared with ^{11}C . These findings reinforce the validity of SPECT quantitation using tracer doses of radioligand binding to neuroreceptor and kinetic modeling methodology. We also found better correlations for measures of benzodiazepine receptor binding in cortical regions than in striatum. This finding is probably related to the lower amounts of specific binding in striatum compared to cortex which translates

into a noisier measure of benzodiazepine receptor binding. The small number of subjects in the current study limits our ability to make firm conclusions about the correlations between measures of benzodiazepine receptor binding obtained with PET and SPECT in individual brain regions.

It is important to validate these techniques, as PET and SPECT are increasingly being used in the quantitation of neuroreceptor binding in studies of neurological and neuropsychiatric disorders. The current results are encouraging from the standpoint of utilization of SPECT in the quantitation of neuroreceptor binding, as PET has traditionally been considered to be the gold standard for quantitation of neuroreceptor binding. SPECT is making rapid strides in quantitative capacity, and it is to be expected that this situation will only improve in the future.

A number of differences distinguish the methodologies employed by PET and SPECT, any of which could introduce differences in quantitation between the two techniques (Bailey et al., 1994). PET neuroreceptor imaging typically uses ^{11}C and ^{18}F as isotopes for radiolabeling receptor compounds, while SPECT most commonly uses ^{123}I . The PET radioisotopes have shorter half-lives (^{11}C , 20 min; ^{18}F , 110 min) than SPECT radioisotopes (^{123}I , 13.2 h). Longer half-lives of SPECT radioisotopes provide more time for radiosynthesis and for measurement of metabolites in plasma. The slower radioactive decay in SPECT vs. PET also makes possible longer imaging times, which facilitate the use of radioligands such as iomazenil with slow washout (Lassen, 1996). However, the use of radioactive carbon (^{11}C) in PET makes it possible to directly incorporate the radioactive moiety into the compound without altering the chemical composition (and potentially the binding properties) of the compound. PET radioisotopes have a higher energy (511 keV) than SPECT (159 keV). Lower energy photons in SPECT mean that there is greater scatter of photons and lower sensitivity to detection compared with PET.

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References

- Abadie, P., Baron, J.C., Bisslerbe, J.C., Boulenger, J.P., Rious, P., Traverre, J.M., Barre, L., Petittaboue, M.C., Zarifian, E., 1992. Central benzodiazepine receptors in human brain: estimation of regional B_{\max} and K_d values with positron emission tomography. *European Journal of Pharmacology* 213, 107–115.
- Abi-Dargham, A., Gandelman, M., Zoghbi, S.S., Laruelle, M., Baldwin, R.M., Randall, P., Zea-Ponce, Y., Charney, D.S., Hoffer, P.B., Innis, R.B., 1995. Reproducibility of SPECT measurement of benzodiazepine receptors in human brain with [^{123}I]iomazenil. *Journal of Nuclear Medicine* 36, 167–175.
- Abi-Dargham, A., Laruelle, M., Seibyl, J., Rattner, Z., Baldwin, R.M., Zoghbi, S.S., Zea-Ponce, Y., Bremner, J.D., Hyde, T.M., Charney, D.S., Hoffer, P.B., Innis, R.B., 1994. SPECT measurement of benzodiazepine receptors in human brain with [^{123}I]iomazenil: kinetic and equilibrium paradigms. *Journal of Nuclear Medicine* 35, 228–238.
- Bailey, D.L., Zito, F., Gilardi, M.-C., Savi, A.R., Fazio, F., Jones, T., 1994. Performance comparison of a state-of-the-art neuro-SPET scanner and a dedicated neuro-PET scanner. *European Journal of Pharmacology* 21, 381–387.
- Baldwin, R.M., Horti, A.G., Bremner, J.D., Stratton, M.D., Dannals, R.F., Ravert, H.T., Zea-Ponce, Y., Ng, C.K., Dey, H.M., Soufer, R., Charney, D.S., Mazza, S.M., Sparks, R.B., Stubbs, J.B., Innis, R.B., 1995. Synthesis and PET imaging of the benzodiazepine receptor tracer [N -methyl- ^{11}C]iomazenil. *Nuclear Medicine and Biology* 22, 659–665.
- Beers, H.-F., Blauenstein, P.A., Hasler, P.H., Delaloye, B., Riccabona, G., Bangerl, I., Hunkeler, W., Bonetti, E.P., Pieri, L., Richards, J.G., Schubiger, P.A., 1990. In vitro and in vivo evaluation of iodine-123 Ro 16-154: a new imaging agent for SPECT investigations of benzodiazepine receptors. *Journal of Nuclear Medicine* 31, 1007–1014.

- Buck, A., Westera, G., von Schulthess, G.K., Burger, C., 1996. Modeling alternatives for cerebral carbon-11-iomazenil kinetics. *Journal of Nuclear Medicine* 37, 699–705.
- Carson, R.E., 1991. The development and application of mathematical models in nuclear medicine. *Journal of Nuclear Medicine* 32, 2206–2208.
- Chang, L.T., 1978. A method for attenuation correction in radionuclide computed tomography. *International Electrical Engineering* 25, 638–639.
- Gandelman, M., Baldwin, R.M., Zoghbi, S.S., Zea-Ponce, Y., Innis, R.B., 1994. Evaluation of ultrafiltration for the free fraction determination of SPECT radiotracers: β -CIT, IBF, and iomazenil. *Journal of Pharmacological Sciences* 83, 1014–1019.
- Huang, S.-C., Phelps, M.E., 1986. Principles of tracer kinetic modeling in positron emission tomography and autoradiography. In: Phelps, M., Mazziotta, J., Schelbert, H. (Eds.), *Positron Emission Tomography and Autoradiography: Principles and Applications for the Brain and Heart*. Raven Press, New York, pp. 287–346.
- Innis, R.B., Al-Tikriti, M.S., Zoghbi, S.S., Baldwin, R.M., Sybirska, E.H., Laruelle, M.A., Malison, R.T., Seibyl, J.P., Zimmermann, R.C., Johnson, E.W., Smith, E.O., Charney, D.S., Heninger, G.R., Woods, S.W., Hoffer, P.B., 1991. SPECT imaging of the benzodiazepine receptor: feasibility of in vivo potency measurements from stepwise displacement curves. *Journal of Nuclear Medicine* 32, 1654–1761.
- Koepp, R.A., Holthof, V.A., Frey, K.A., Kilbourn, M.R., Kuhl, D.E., 1991. Compartmental analysis of [^{11}C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism* 11, 735–744.
- Laruelle, M., Baldwin, R.M., Rattner, A., Al-Tikriti, M.S., Zea-Ponce, Y., Zoghbi, S.S., Charney, D.S., Price, J.C., Frost, J.J., Hoffer, P.B., Innis, R.B., 1994. SPECT quantification of [^{123}I]iomazenil binding to benzodiazepine receptors in nonhuman primates. I. Kinetic modeling of single bolus experiments. *Journal of Cerebral Blood Flow and Metabolism* 14, 439–452.
- Lassen, N.A., 1996. A reappraisal of the relative merits of SPET and PET in the quantitation of neuroreceptors: the advantage of a longer half-life! *European Journal of Nuclear Medicine* 23, 1–4.
- Mulaney, N.A., Gould, L.K., Hartz, R.K., Hitchens, R.E., Wong, W.H., Bristow, D., Adler, S., Philippe, E.A., Bendrien, B., Sanders, M., Gibbs, B., 1990. Design and performance of Posicam 6.5 BGO Positron camera. *Journal of Nuclear Medicine* 31, 610–616.
- Pike, V.W., Halldin, C., Crouzel, C., Barre, L., Nutt, D.J., Osman, S., Shah, F., Turton, D.R., Waters, S.L., 1993. Radioligands for PET studies of central benzodiazepine receptors and PK (peripheral benzodiazepine) binding sites — current status. *Nuclear Medicine and Biology* 20, 503–525.
- Price, J.C., Mayberg, H.S., Dannals, R.F., Wilson, A.A., Ravert, H.T., Sadzot, B., Rattner, Z., Kimball, A., Feldman, M.A., Frost, J.J., 1993. Measurement of benzodiazepine receptor number and affinity in humans using tracer kinetic modeling, positron emission tomography, and [^{11}C]flumazenil. *Journal of Cerebral Blood Flow and Metabolism* 13, 656–667.
- Spitzer, R.L., Williams, J.B.W., Gibbon, M., 1987. *Structured Clinical Interview for DSM-III-R*. New York State Psychiatric Institute, Biometrics Research Department, New York.
- Sybirska, E., Seibyl, J.P., Bremner, J.D., Baldwin, R.M., Al-Tikriti, M.S., Bradberry, C., Malison, R.T., Zea-Ponce, Y., Zoghbi, S., Doring, M., Goddard, A.W., Woods, S.W., Hoffer, P.B., Charney, D.S., Innis, R.B., 1993. [^{123}I]iomazenil SPECT imaging demonstrates significant benzodiazepine receptor reserve in human and nonhuman primate brain. *Neuropharmacology* 32, 671–680.
- Westera, G., Buck, A., Burger, C., Leenders, K.L., von Schulthess, G.K., Schubiger, A.P., 1996. Carbon-11 and iodine-123 labeled iomazenil: a direct PET-SPECT comparison. *European Journal of Nuclear Medicine* 23, 5–12.
- Westera, G., Eberle, I., Hunkeler, W., 1993. The production of [^{11}C]iomazenil. *Journal of Laboratory Compounds and Radiopharmaceuticals* 32, 169–170.
- Zea-Ponce, Y., Baldwin, R.M., Seibyl, J.P., Zoghbi, S.S., Innis, R.B., 1994. Formation of 1- ^{123}I iodobutane in iododestannylation: implications for the reaction mechanism. *Applied Radiation Isotopes* 45, 63–68.
- Zoghbi, S.S., Baldwin, R.M., Seibyl, J.P., Al-Tikriti, M.S., Zea-Ponce, Y., Laruelle, M., Sybirska, E.H., Woods, S.W., Goddard, A.W., Malison, R.T., Zimmerman, R., Charney, D.S., Smith, E.O., Hoffer, P.B., Innis, R.B., 1992. Pharmacokinetics of the SPECT benzodiazepine radioligand [^{123}I]iomazenil in human and nonhuman primates. *Nuclear Medicine and Biology* 19, 881–888.