

Kinetic Modeling of Benzodiazepine Receptor Binding with PET and High Specific Activity [¹¹C]Iomazenil in Healthy Human Subjects

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ABSTRACT Quantitation of the PET benzodiazepine receptor antagonist, [¹¹C]Iomazenil, using low specific activity radioligand was recently described. The purpose of this study was to quantitate benzodiazepine receptor binding in human subjects using PET and high specific activity [¹¹C]Iomazenil. Six healthy human subjects underwent PET imaging following a bolus injection of high specific activity (>100 Ci/mmol) [¹¹C]Iomazenil. Arterial samples were collected at multiple time points after injection for measurement of unmetabolized total and nonprotein-bound parent compound in plasma. Time activity curves of radioligand concentration in brain and plasma were analyzed using two and three compartment model. Kinetic rate constants of transfer of radioligand between plasma, nonspecifically bound brain tissue, and specifically bound brain tissue compartments were fitted to the model. Values for fitted kinetic rate constants were used in the calculation of measures of benzodiazepine receptor binding, including binding potential (the ratio of receptor density to affinity), and product of BP and the fraction of free nonprotein-bound parent compound (V_3'). Use of the three compartment model improved the goodness of fit in comparison to the two compartment model. Values for kinetic rate constants and measures of benzodiazepine receptor binding, including BP and V_3' , were similar to results obtained with the SPECT radioligand [¹²³I]iomazenil, and a prior report with low specific activity [¹¹C]Iomazenil. Kinetic modeling using the three compartment model with PET and high specific activity [¹¹C]Iomazenil provides a reliable measure of benzodiazepine receptor binding. **Synapse 35:68–77, 2000.**

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INTRODUCTION

Quantitation of benzodiazepine receptor binding is an important tool in the study of neuropsychiatric and neurological disorders (reviewed in Pike et al., 1993). Several studies used positron emission tomography (PET) in the quantitation of benzodiazepine receptor binding in human brain. Initially, benzodiazepine receptor binding quantification was performed with the PET benzodiazepine receptor ligand [¹¹C]flumazenil (Ro 15–1788) (Blomqvist et al., 1990; Frey et al., 1991; Holthoff et al., 1991; Koeppe et al., 1991, 1996; Pappata et al., 1988; Persson et al., 1985; Samson et al., 1985; Shinto et al., 1986). These studies provided measures of the binding potential, which is the ratio of benzo-

diazepine receptor number (B_{max}) to receptor affinity (K_D) (Abadie et al., 1992; Koeppe et al., 1991) as well as separate measurements of receptor number (B_{max}) and affinity (K_D) (Brouillet et al., 1990; Millet et al., 1995; Price et al., 1993). Subsequently, SPECT methods have been developed for quantitation of benzodiazepine receptor binding in humans subjects using [¹²³I]iomazenil

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and kinetic and equilibrium methods (Abi-Dargham et al., 1994, 1995; Bear et al., 1990; Innis et al., 1991; Laruelle et al., 1994; Sybirska et al., 1993). Recently, methods were developed to enable quantification of benzodiazepine receptor binding with SPECT [¹²³I]iomazenil that do not require arterial blood sampling and complicated image acquisition protocols (Onishi et al., 1995, 1996a,b). Given the general availability of SPECT, these methods should make clinical studies of the benzodiazepine receptor feasible in a large number of centers (Savic et al., 1988; Schubiger et al., 1991).

Methods for quantification of neuroreceptor binding have been more fully developed with PET than with SPECT, and SPECT-based techniques need to be validated with PET (Carson, 1991). Iomazenil was recently labeled with ¹¹C for imaging with PET (Baldwin et al., 1995; Westera et al., 1993). It is, therefore, an ideal ligand for comparison of quantitation with SPECT and PET (Westera et al., 1996). Iomazenil also has some advantages over the other commonly utilized ligand, flumazenil, in quantitation of benzodiazepine receptors in living human brain. For instance, iomazenil has a much higher ratio of specific to nonspecific binding (40:1) (Sybirska et al., 1993) than flumazenil.

The only studies to date to quantitate benzodiazepine receptor binding with PET and [¹¹C]iomazenil used low specific activity (11–25 Ci/mmol) radioligand (Buck et al., 1996; Westera et al., 1996). Radioligand with specific activity in this range can be associated with significant receptor binding, on the order of 10–30%. At this level of receptor binding, the assumption of negligible receptor binding that underlies tracer kinetic modeling for quantitation of neuroreceptor number may be violated. With significant receptor occupancy by the injected radioligand, the number of receptors available for binding will vary as a function of time, affecting estimates of parameters related to transfer of ligand on and off receptors, and related estimates of receptor binding (Buck et al., 1996). We, therefore, assessed methods for quantitation of benzodiazepine receptor binding using PET and high specific activity [¹¹C]iomazenil in healthy human subjects. In this study, methods for quantitation of benzodiazepine receptor binding in human subjects using PET [¹¹C]iomazenil and two and three compartment models are reported.

MATERIALS AND METHODS:

Subjects

The subjects were composed of six healthy white males without current or past histories of medical or psychiatric illness based on the SCID for non-patients interview (Spitzer et al., 1987), physical examination, and laboratory screening. Age of subjects ranged from 18 to 27. Subjects were recruited by newspaper advertisement. Subjects were free of all medications and alcohol for at least 4 weeks prior to the study, and had no lifetime history of benzodiazepine use. All subjects

were white, male, and right-handed. 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.

Radiolabelling of Iomazenil With ¹¹C

[*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 minute at 80°C and purified by HPLC. The product was obtained with a radiochemical yield of 98% and specific activity 100–500 Ci/mmol as measured at the time of injection. These methods have been described in greater detail in a previous publication (Baldwin et al., 1995).

PET Imaging Methods

At the beginning of the PET imaging session, subjects were placed in a Posicam camera (Positron Corporation) with an intravenous and intraarterial line in place. The Posicam is a 21-slice camera with a 5.125-mm inter-slice 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 transaxial 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 containing 1–2 μCi ¹⁸F were attached on both sides of the subjects 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. Initially an attenuation 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 intravenous bolus over 30 seconds followed by PET imaging in list mode for 105 minutes. Arterial samples were obtained every minute for the first four minutes after injection with a peristaltic pump (Harvard 2501–001, South Natick, MA), then manually at intervals of 6, 8, 12, 16, 20, 30, 45, 60, 75, 90, and 105 minutes after injection.

PET Image Reconstruction and Analysis

PET list mode data was broken into images of 30 seconds duration for the first 2 minutes, then of two and a half minute duration for the next 18 minutes, then of 5-minute duration for the rest of the period of acquisition. Images were reconstructed using a Butterworth filter (order = 10; cutoff = .306) on a 128 x 128 x 21 matrix (pixel size 1.9 mm x 1.9 mm, slice thickness = 5.125 mm). Images were inspected for movement dur-

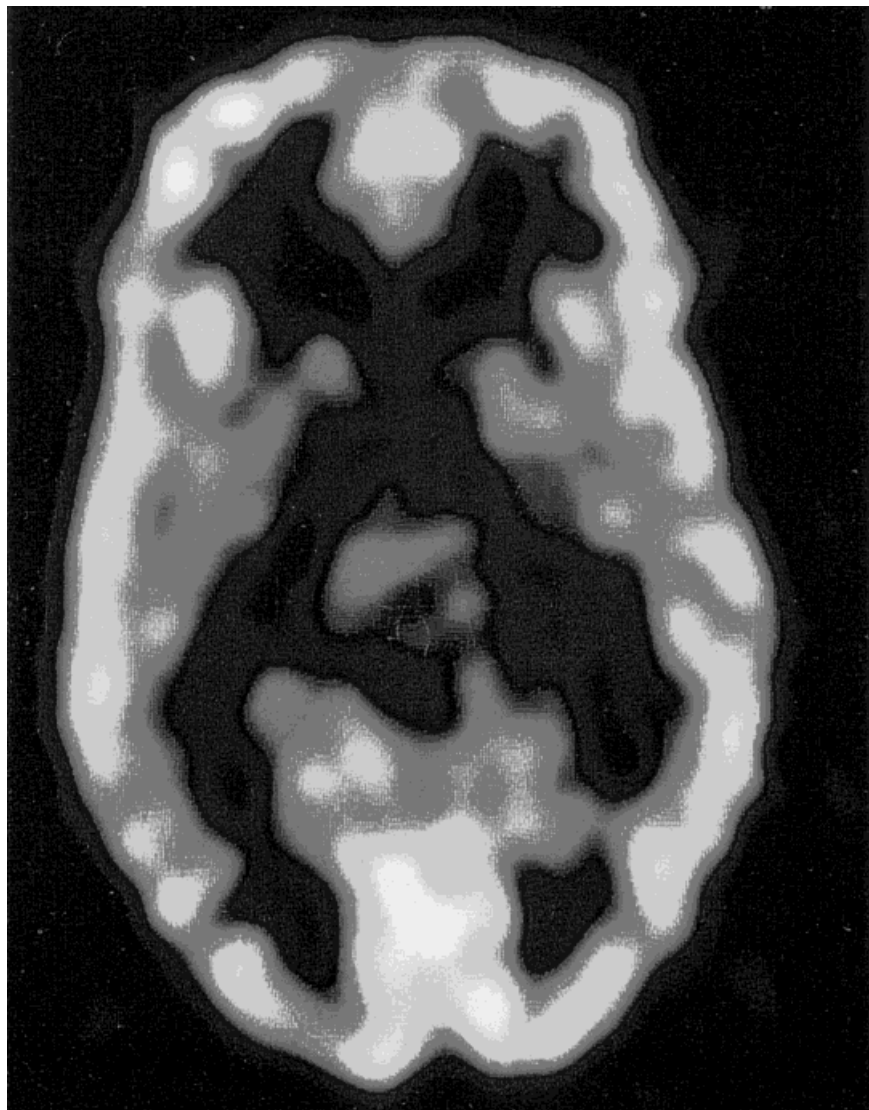


Fig. 1. Transaxial image of [^{11}C]iomazenil binding in human brain 30–50 minutes after a bolus injection of radioligand. There is uniform distribution of radioligand throughout cerebral cortex, with a 20:1 distribution of binding in gray matter versus white matter.

ing the imaging session by visualization of location of fiducial markers and images were manually realigned to correct for motion artifact if needed. 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) drew ROIs over areas of radioligand uptake in cortical areas using the boundaries of cortical uptake to determine the outline of the ROI. Since there is such a strong definition between cortical grey and white matter with this radioligand (due to its 40:1 grey to white matter binding ratio, Fig. 1), the grey-white matter boundary is easily visualized and was used to determine the boundary of the ROI. Mean of activity in the three slices and left and right ROIs were determined for generation of the final tissue activity curve for each ROIs (frontal, temporal, occipital cortex, and striatum). A 12-cm cylindrical fluid filled phantom with a known

amount of ^{18}F was scanned for the determination of a calibration factor for conversion of radioactivity in the PET images (cpm) into absolute units of radioactivity (μCi).

Arterial Plasma Analysis

Plasma was separated by centrifugation and analyzed for concentration of radioligand and metabolites in plasma by solvent extraction as previously described (Baldwin et al., 1995; Zoghbi et al., 1992) to obtain metabolite-corrected parent plasma activity in units of $\mu\text{Ci}/\text{mL}$. 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 exponentials were determined. Initial volume of distribution was calculated as the injected dose divided by the sum of the zero time intercepts.

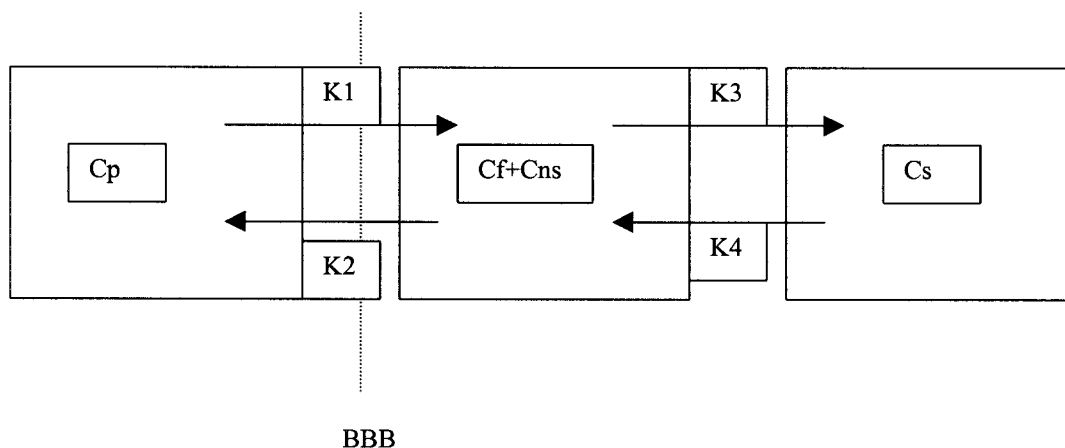


Fig. 2. Three compartment kinetic model. The three compartments include free ligand in plasma (C_p), free (Cf) and non-specifically bound (Cns) ligand in brain, and specifically bound (Cs) to receptor ligand in brain. Two compartment model includes free ligand in plasma and ligand in brain.

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

Data Analysis and Kinetic Modeling

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. The data were utilized in the assessment of kinetic parameters for rate of transfer between plasma and brain (nonspecifically bound and specifically bound to receptor) using two and three compartment models (Sandberg, 1978). The two compartment model includes compartments for arterial plasma (C_a) and brain (C_T). The three compartment model includes compartments for arterial plasma (C_a), free and nonspecifically bound ligand in brain (C_2), and ligand in brain that is specifically bound to receptor (C_3) (Fig. 2). The volume of distribution of a compartment i relative to the free tracer in arterial plasma ($V_i \text{ ml g}^{-1}$) is defined as the equilibrium ratio of the tracer concentration in compartment i to the free tracer concentration in the arterial plasma ($V_i = C_i / (f_1 C_a)$). Therefore, V_2 represents the equilibrium distribution volume of free and nonspecifically bound radioligand, V_3 is the equilibrium distribution volume of radioligand specifically bound to receptor in the brain, and V_T is the total equilibrium distribution volume. With tracer doses V_3 and V_T are close approximations of binding potential (BP) (the ratio of receptor density to affinity). The volume of distribution of a compartment i relative to the total tracer in arterial plasma ($V_i \text{ ml g}^{-1}$) is defined as the equilibrium ratio of the tracer concentration in compartment i to the total tracer concentration in the arterial plasma ($V_i' = C_i / C_a$) and ($V_i' = V_i f_1$).

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., 1994, 1995).

Equilibrium distribution volumes are calculated from ratios of the rate constants of transfer of radioligand between compartments. In the two compartment model, K_1 represents rate of transfer from blood to brain; k_2 rate of transfer from brain to blood; and f_1 is the fraction of parent compound in plasma that is non-protein bound and available for uptake into the brain. In the three compartment model, 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 nonspecific or unbound to specifically bound radioligand; and k_4 rate of transfer from specifically bound to nonspecifically bound equilibrium distribution volumes are calculated from kinetic rate constants estimated with compartmental modeling. Compartmental modeling was performed with the Statistical Analysis and Modeling-II (SAAM-II) program (Seattle, WA). Values for K_1 - k_4 were determined by fitting the models to the time activity curves for the various regions of interest and fitted curves of total parent compound in plasma as the input function, and minimizing sum of squares of the residuals. Goodness of fit was assessed with the Akaike Information Criterion (AIC) (Akaike, 1974) and Bayesian Information Criterion (BIC). 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 nondisplaceable compartment (Abi-Dargham et al., 1994). In these experiments there were no significant differences between regions in the nonspecific volume of distribution;

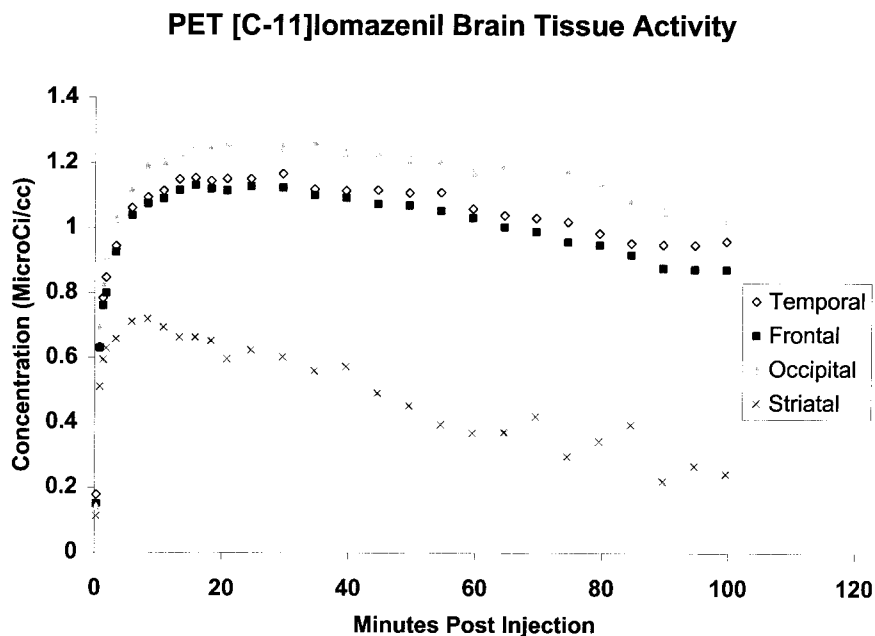


Fig. 3. Time activity curves for concentration of [¹¹C]iomazenil in temporal, frontal, occipital, and striatal cortex following bolus injection of radioligand in a representative subject. There is a rapid uptake of tracer in brain with a peak concentration of activity at 20 minutes after injection, followed by a slow washout of activity from these areas.

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. In the two compartment model, (V_T) is equal to ($V_2 + V_3$, or $K_1/k_2 \cdot f_1$) (Laruelle et al., 1994). V_2 in the three-compartment model is equal to ($K_1/(k_2 \cdot f_1)$), and V_3 is equal to the binding potential (BP), or ($K_1 \cdot k_3/k_2 \cdot k_4 \cdot f_1$) (Mintun et al., 1984).

RESULTS

PET Imaging

Radioligand distributed throughout cortical regions, with lesser uptake in striatum, and essentially no uptake in white matter regions following bolus injection of radioligand (Fig. 1). Activity in brain for temporal, frontal, occipital cortex, and striatum is shown in a representative subject for PET in Figure 3. The time activity curve showed a rapid uptake of radioligand in cortical tissue, with most of the uptake occurring in the first 10 minutes, and peak uptake at approximately 20–30 minutes, followed by a period of delayed washout.

Arterial Plasma Analysis

Activity of radioligand in plasma determined from arterial samples over multiple time points after injection in a representative subject is shown in Figure 4. There was rapid clearance of radioligand from plasma after injection. Mean values for the half lives of the exponentials ($=\ln 2/\lambda_i$) determined from triexponential fits of concentration of total parent compound in plasma after injection were as follows: first half life (0.92 ± 0.24

minutes), second half life (14.04 ± 7.66 minutes), and terminal half-life ($11,575.05 \pm 17,873.79$ minutes). Estimates of the terminal half lives of the arterial plasma data were considered to be highly unstable due to the low counts at the later time points. Mean values for the y-intercept of the three components of the exponential for the arterial data were as follows: first component (3.85 ± 2.29), second component (0.09 ± 0.04), and third component (0.05 ± 0.03) of the exponential. Values for the initial volume of distribution were (45.23 ± 13.73 liter/kg). Values determined for the fraction of non-protein bound radioligand (f_1) were 0.37 ± 0.01 .

PET Data Analysis and Kinetic Modeling

Results from fits to the PET data using nonlinear regression with two and three compartment models are displayed in Tables I and II. Data were fitted to obtain estimates of kinetic rate constants and derived measures of benzodiazepine receptor binding (binding potential- V_3 , and the related measure V_3' , product of binding potential and the fraction of nonprotein-bound plasma parent compound- f_1). Values for benzodiazepine receptor binding in the current study with high specific activity [¹¹C]iomazenil were similar to previous PET studies using low specific activity [¹¹C]iomazenil (Buck et al., 1996), and previous SPECT studies using [¹²³I]-iomazenil (Abi-Dargham et al., 1994, 1995; Laruelle et al., 1994). Superior fits were obtained using three compartment model to two compartment model for all regions, as demonstrated by significantly lower values for Akaike Information Criterion (AIC) in three compartment vs. two compartment models ($P < 0.05$) (Table III). These findings are consistent with a better descrip-

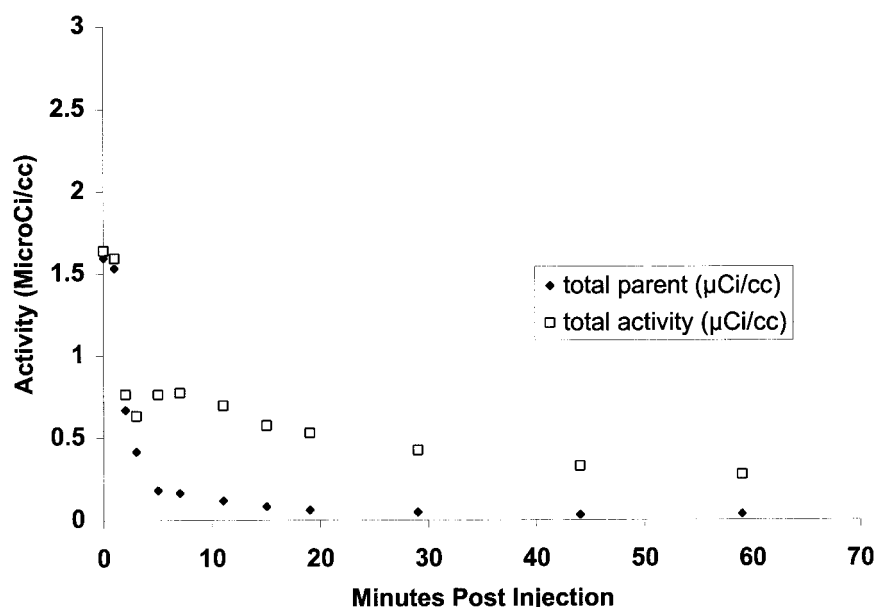
PET [¹¹C]Iomazenil Arterial Plasma Activity

Fig. 4. Concentration of total parent [¹¹C]iomazenil and total radioactivity in plasma after bolus injection of radioligand. There is a rapid clearance of [¹¹C]iomazenil from plasma within the first 10 minutes of injection.

TABLE I. Estimates of K_1 , k_2 , VT , and VT' using two compartment model

Region	K_1			k_2			VT			VT'		
	ml g ⁻¹ min ⁻¹	SD	COV	min ⁻¹	SD	COV	ml g ⁻¹	SD	COV	ml g ⁻¹	SD	COV
Occipital	0.222	0.065	29.4%	0.011	0.001	4.5%	46.037	17.580	38.2%	16.953	5.802	34.2%
Frontal	0.184	0.061	33.5%	0.012	0.001	7.3%	42.015	16.577	39.5%	15.451	5.448	35.3%
Temporal	0.196	0.066	33.5%	0.012	0.001	7.7%	44.024	14.183	32.2%	16.119	4.973	30.9%
Striatum	0.174	0.053	30.3%	0.028	0.006	21.4%	18.246	8.212	45.0%	6.612	2.843	43.0%

TABLE II. Estimates of K_1 - k_4 , V_3 , V_3' , VT and VT' with three compartment model

Region	K_1			k_2			k_3			k_4		
	ml g ⁻¹ min ⁻¹	SD	COV	min ⁻¹	SD	COV	min ⁻¹	SD	COV	min ⁻¹	SD	COV
Occipital	0.344	0.130	37.8%	0.108	0.041	37.8%	0.094	0.027	28.3%	0.014	0.003	21.6%
Frontal	0.306	0.107	35.0%	0.096	0.033	35.0%	0.084	0.025	30.3%	0.014	0.003	21.2%
Temporal	0.311	0.125	40.1%	0.097	0.039	40.1%	0.093	0.035	37.8%	0.016	0.003	18.6%
Striatum	0.249	0.067	26.9%	0.078	0.021	26.9%	0.035	0.021	58.5%	0.029	0.020	71.9%

Region	V_3			V_3'			VT			VT'		
	ml g ⁻¹	SD	COV	ml g ⁻¹	SD	COV	ml g ⁻¹	SD	COV	ml g ⁻¹	SD	COV
Occipital	63.757	22.602	35.5%	25.737	5.332	20.7%	72.506	22.877	31.6%	26.486	7.952	30.0%
Frontal	55.629	19.351	34.8%	20.285	6.671	32.9%	64.378	19.644	30.5%	23.485	6.671	28.4%
Temporal	51.168	20.996	41.0%	18.659	7.436	39.9%	59.917	21.281	35.5%	21.947	7.570	34.5%
Striatum	11.755	6.429	54.7%	4.226	2.272	53.8%	20.628	6.505	31.5%	7.426	2.272	30.6%

TABLE III. Estimates of goodness of fit with two and three compartment models

Region	Two Compartment Model				Three Compartment Model			
	AIC	SD	BIC	SD	AIC	SD	BIC	SD
Occipital	2.263	0.332	2.312	0.332	1.609	0.278	1.681	0.279
Frontal	2.192	0.302	2.240	0.302	1.664	0.238	1.618	0.271
Temporal	2.150	0.343	2.197	0.343	1.585	0.255	1.657	0.255
Striatum	2.481	0.347	2.528	0.347	1.648	0.472	1.720	0.472

AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria

tion of the physiology of benzodiazepine receptor binding by iomazenil for three compartment vs. two compartment models (Buck et al., 1996; Laruelle et al., 1994).

Parameter and distribution volume (VT' and V_3') estimates for occipital cortex as a function of the duration of data used in the fits are shown in Figures 5

Stability of K_4 as a Function of Minutes of Data Included in Three Compartment Model Fit

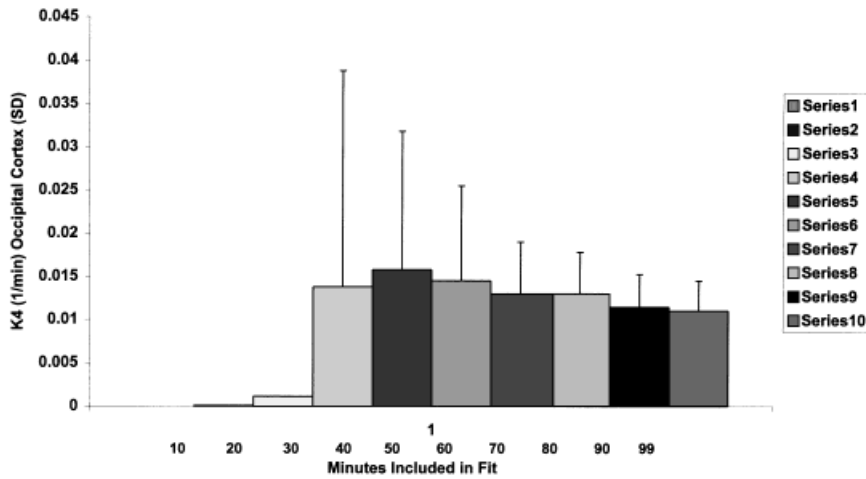


Fig. 5. Stability of K_4 as a function of minutes of data included in the fit. With decreasing scan time included in the fit, there was increasing variability in the estimate of K_4 , but the values of K_4 were unchanged with scan times of 40 minutes or more. With less than 40 minutes of data estimated values of K_4 were highly aberrant.

Stability of VT' for Two Compartment Model As a Function of Minutes Included in Fit

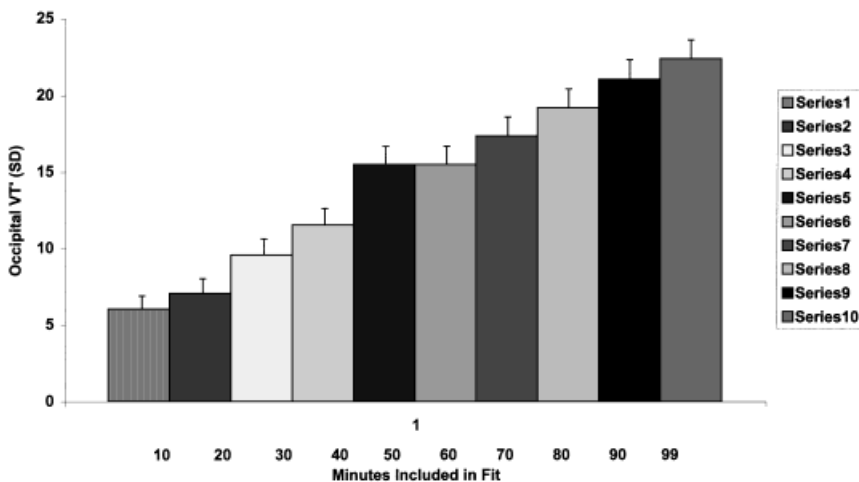


Fig. 6. Estimates of distribution volume (VT') determined with the two compartment model as a function of minutes of data included in the fit. With decreasing scan time included in the fit, there was a progressive decrease in estimates of VT' based on the two compartment model.

to 7. Estimates were performed with 99 minutes of data, then repeated with consecutively 10 minutes less data, until there were only 10 minutes of data. In Figure 5, mean values (\pm SD) of k_4 as a function of minutes of data included in the fit are displayed. There was increasing variability in the estimate of the parameter with decreased length of scanning time. Mean values for k_4 , however, were essentially unchanged, with more than 30 minutes of data included in the fit. With less than 30 minutes, the values for k_4 became highly aberrant. Similar results were obtained for other cortical regions (data not shown). In Figure 6, values of the estimate of binding (VT') based on the two compartment model are shown as a function of minutes of data included in the fit. There were continuous decreases in the estimated value of VT' with decreased length of time data included in the fit. With the three compart-

ment model, on the other hand, values for $V3'$ were not appreciably changed with more than 30 minutes of data included in the fit, although there was a progressive decrease in reliability of the estimate (Fig. 7). With less than 30 minutes of data, the values for $V3'$ were highly aberrant.

DISCUSSION

PET measurement of benzodiazepine receptor binding with high specific activity [^{11}C]iomazenil yielded similar result to previous studies using PET with low specific activity [^{11}C]iomazenil (Buck et al., 1996). These findings confirm the utility of [^{11}C]iomazenil in imaging of the benzodiazepine receptor in human brain. [^{11}C]iomazenil is useful in that it can be used in studies comparing quantitation of PET and SPECT in the same

Estimates of V3' Based on Three Compartment Model As A Function of Scan Duration

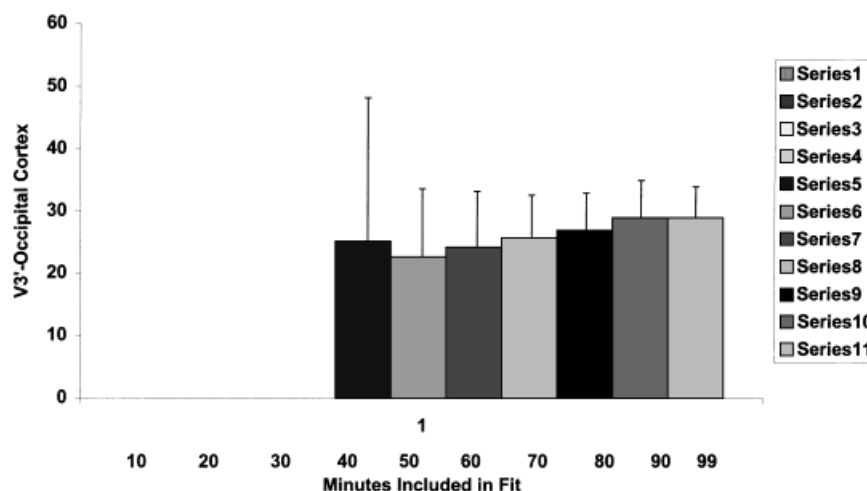


Fig. 7. Stability of distribution volume (V_3') based on the three compartment model as a function of minutes of data included in the fit. With decreasing scan time included in the fit, there was increasing variability in the estimate of V_3' based on the three compartment model, but the values of V_3' were unchanged with scan times of 40 minutes or more. With less than 40 minutes of data estimated values of V_3' were highly aberrant.

human subjects (Westera et al., 1996; Bremner et al., unpublished data).

A previous study examining benzodiazepine receptor binding with [¹¹C]iomazenil used low specific activity radioligand (11–25 Ci/mmol) (Buck et al., 1996) while the current study used high specific activity radioligand (>100 Ci/mmol). With specific activity in the lower range, there is the possibility that there may be significant receptor occupancy by radioligand, on the order of 10–30%. With this level of receptor occupancy, the injected radioligand may occupy receptor sites in a time-dependent fashion, affecting parameter estimates related to transfer of ligand on and off of the receptor. Buck et al. (1996) hypothesized that the use of low specific activity radioligand may lead to an underestimation of transfer rates of ligand onto receptor (K_3). Values for K_3 based on kinetic modeling with low specific activity radioligand, however, were equal to or greater than values for K_3 based on kinetic modeling with high specific activity radioligand reported in the current study. Perhaps of more relevance, however, is the finding that values for distribution volumes were essentially identical based on kinetic modeling performed with low and high specific activity radioligand. This is important, since most clinical studies will use distribution volumes as outcome measures, rather than values of the individual parameters that are used in the derivation of distribution volume values.

Use of the three compartment model yielded the best fits to the data for all regions examined in this study. Significantly better fits were obtained as determined by the Akaike Information Criteria (AIC), which adjusts for differences in the residual sum of squares obtained after convergence of the fit, which are related to the additional number of parameters in the three compartment in comparison to the two compartment model. These findings indicate that the three compartment

model provides a better description of the physiology of benzodiazepine receptor binding with [¹¹C]iomazenil than the two compartment model (Buck et al., 1996; Laruelle et al., 1994). This is in contrast to kinetic modeling of [¹¹C]flumazenil, in which the two compartment model was adequate (Holthoff et al., 1991; Koeppe et al., 1991). This is probably due to the greater value of K_4 , which indicates a more rapid exchange of ligand between specific and nonspecifically bound compartments.

Results for identifiability of distribution volume (V_T') and K_4 as a function of scan duration were consistent with previous reports using low specific activity [¹¹C]iomazenil (Buck et al., 1996) and [¹²³I]iomazenil (Laruelle et al., 1994). Consistent with those previous reports, in the current study, scan duration of less than 100 minutes yielded progressive underestimations of distribution volume (V_T') measured with the two compartment model. On the other hand, estimates of V_3' based on the three compartment model were essentially unchanged with decreases in scan time down to 30 minutes. This illustrates an additional disadvantage of the two compartment model for [¹¹C]iomazenil. For the three compartment model, k_4 was identified with reasonable certainty with more than 30 minutes of data, however, estimates became increasingly unreliable with less than 30 minutes of data. Values of K_4 in the 0.014–0.29 min^{-1} range were closer to results obtained with previous [¹²³I]iomazenil studies (0.014–0.034 min^{-1}) than to values obtained with low specific activity [¹¹C]iomazenil (0.04–0.06 min^{-1}). As can be seen from the time activity curves for radioligand concentration in cortical brain tissue, however, there is an extremely slow rate of washout of tracer from the brain over time, consistent with the low values of K_4 . In fact, similar values of K_4 have been considered to be essentially equivalent to zero in kinetic modeling studies of [¹⁸F]-

2-fluoro-2-deoxyglucose (FDG) (Sokoloff et al., 1977). One has to question, therefore, the meaning of differences in values of this parameter on the order of 2–3%.

CONCLUSIONS

Quantitation of benzodiazepine receptor binding with PET and a single bolus of high specific activity [¹¹C]iomazenil yields estimates of receptor binding similar to those seen with low specific activity [¹¹C]iomazenil and SPECT quantitation of [¹²³I]iomazenil. Kinetic modeling is best performed using a three compartment model with greater than 30 minutes of PET acquisition time. [¹¹C]iomazenil is a promising tracer for quantitation of benzodiazepine receptor binding for direct comparisons with SPECT [¹²³I]iomazenil quantitation of benzodiazepine receptor binding.

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