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Compartmental Modeling and Simplified Quantification of [^{11}C]sertraline Distribution in Human Brain

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Sertraline hydrochloride (Zoloft®, Pfizer) is an antidepressant drug of the selective serotonin reuptake inhibitor (SSRI). The aims of this study were evaluating its *in vivo* distribution and kinetic models in human brain. Also, this study was to determine optimal scan duration of dynamic positron emission tomography (PET) for accurate [^{11}C]sertraline kinetic parameters and the feasibility of semi-quantitative approach for assessing distribution volume ratio (DVR). [^{11}C]sertraline dynamic PET and magnetic resonance imaging (MRI) scans were performed in 5 healthy males. Blood sampling were collected for the input function. Tissue time-activity curves (TAC) were obtained in 7 brain regions using MRI. Goodness-of-fit for TAC using simple tissue compartment model (2C2P) and 3-compartment models with irreversible (3C3P) and reversible (3C4P) were compared. Total distribution volume (DV) for each region of interest (ROI) and DVR were calculated. Also, ratio between the standard uptake value (SUV) of each ROI and that of cerebellum (SUVr) was computed and correlated with the DVR. Akaike information criteria analysis showed that the 2C2P was the most suitable model. Average values of K_1 (mL/min/g) and k_2 (1/min) were 0.54 and 0.012 in putamen. PET scan time longer than 50 min was required for the accurate estimation of DV. SUVr in 50-90 min was well correlated with DVR.

Key words: Kinetic modeling, Serotonin transporters, Pharmacokinetics, PET, [^{11}C]sertraline, Microdose

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INTRODUCTION

The strong merit of positron emission tomography (PET) imaging of a radiolabeled pharmaceutical or tracer would be a straightforward visualization of their biodistribution (Valk et al., 2003; Shields and Price, 2007; Fazaeli et al., 2011; Zhu et al., 2011). In addition, the quantitative analysis of those PET data can provide clues to understand their kinetics in the body (Lee et al., 2005; Shields and Price, 2007; Kim et al., 2008a, 2008b). Pharmacokinetic-pharmacodynamic modeling study using a new pharmaceutical that is radiolabeled is also useful for suggesting initial administration strategy in further preclinical and clinical studies (Lim et al., 2007).

Serotonin transmission system has been studied for a long time because it is highly related to affective disorders and selective serotonin reuptake inhibitors (SSRI) are commonly used medications (Kapur and Remington, 1996; Kim et al., 2002; Sanacora et al., 2002; Munhoz, 2004; Dahl et al., 2005; Esposito, 2006; Voineskos et al., 2007; Dayan and Huys, 2008). Sertraline hydrochloride (Zoloft, Lustral), produced by Pfizer in 1991, is an anti-depressant medication which is widely used as a SSRI (Kim et al., 2002; Munhoz, 2004). Sertraline hydrochloride vitalizes serotonin or increases

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the time that serotonin is available in the synaptic cleft (Kim et al., 2002). Although sertraline is a widely used drug for patients, there have been no studies to investigate its kinetics in living human brain (Kapur and Remington, 1996).

In this study, dynamic brain PET studies were performed in healthy volunteers using [^{11}C]sertraline to investigate its biodistribution and tracer kinetic model in brain tissues. Arterial blood samples were obtained and time-activity curves from several brain regions were analyzed. We selected the best PET kinetics models for [^{11}C]sertraline based on Akaike Information Criterion (AIC) (Yamaoka et al., 1978; Ludden et al., 1994; Kim et al., 2008). Also, this study was to determine the optimal scan duration of dynamic PET studies for the accurate estimation of kinetic parameters and the feasibility of semi-quantitative approach without arterial blood sampling for the assessment of distribution volume ratio (DVR) in human brain.

MATERIALS AND METHODS

Synthesis of [^{11}C]sertraline

One mg of norsertraline was separated in a 4-mL vial and dissolved in DMF (0.1 mL). 5 μL of NaOH (5 μmol) was added in the loop of a HPLC. The mixture was injected into a stainless steel loop (2 mL) of the prep HPLC by a Hamilton syringe. [^{11}C]CH3OTf was blown to the loop by nitrogen gas (99.999%) at 20 mL/min for 3 min. [^{11}C]sertraline was separated by a prep-HPLC (column: Waters XTerra RP-8, 10 × 250 mm, 10 μm; Waters; eluent-EtOH 55% in 10 mM phosphate buffer at pH 7; flow rate: 3 mL/min; room temperature; 215 nm wavelength). The retention time of [^{11}C]sertraline was 28 min.

Study population

This clinical study was approved by the Institutional Review Board in Seoul National University Hospital, Seoul, Korea. Five healthy male volunteers were enrolled in this study (mean age, 32.4 years; range, 21-43 years). None of them had a history of mental illness and all of them passed a screening test, including urine and blood test for selecting physically healthy volunteers.

Image acquisition

PET study was performed in 2D mode on the whole body scanner, ECAT Exact 47 (Siemens). Before the scan started, catheters were placed in the volunteer's vein in arm for injecting radiotracer, and in the artery of the contralateral arm for blood sampling by an anesthesiologist. Dynamic [^{11}C]sertraline PET scan that was acquired for 90 (n=3) or 120 min (n=2) with a variable frame duration (15 s × 8, 30 s × 16, 60 s × 10, 240 s × 10, and 300 s × 6 or 12) were initiated immediately after injection of 690.42 MBq (569.8-832.5 MBq) [^{11}C]sertraline. Images were reconstructed as 128 × 128 × 47 matrices of 2.570 × 2.570 × 3.375 mm voxel by using a filtered back projection algorithm (Fig. 1).

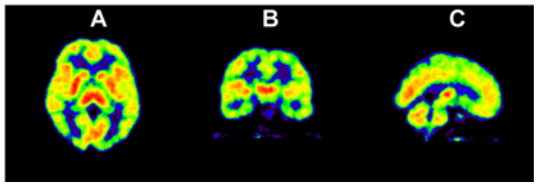

Fig. 1. [^{11}C]sertraline PET image of human brain (0-90 min). Transaxial (**A**), Coronal (**B**), Sagittal (**C**).

To obtain the calibration factor between the PET scanner and dose calibrator, a phantom experiment was performed. After measuring the radioactivity in a dose calibrator, a uniform phantom (6,281 mL) with 51 MBq ^{18}F was scanned in the PET scanner during 60 min. Because the half-life of ^{11}C is too short to acquire sufficient counts in the scanner, we used ^{18}F.

To obtain the anatomical information of brain, all the volunteers underwent MRI scans. T1-weighted 3D SPGR MRI images (0.94 × 0.94 × 1.00 mm pixel size) were obtained using a GE 3.0T VH/i SIGNA EXCITE E2M4 scanner (GE).

Blood sampling and analysis

For acquiring an arterial input time-activity curve (input function), we took blood samples during the PET scan. We sampled blood continuously for the first 2 min and the next time points were 2.5, 3, 4, 5, 6, 8, 10, 15, 30, 55, 70, and 90 min. The blood was collected in 2-mL samples in heparin-sprayed vacuum tubes. Each tube was centrifuged at a speed 3,000 rpm. After centrifugation, only the plasma layer (0.4 mL) was pipetted to measure the activity on a γ-counter. We also measured each plasma weight for normalization to reduce the activity error. We opened the 511 ± 50 keV energy window for [^{11}C]sertraline at the γ-counter with a ^{11}C attenuation correction mode.

Tissue time-activity curves

Static PET image was generated by summing all dynamic PET frames and coregistered with magnetic resonance (MR) image of same individual. The MR image of each individual was spatially normalized into T1 template using SPM software, and the transformation parameters of spatial normalization were applied to each frame of dynamic PET data.

The probability map of each anatomical region in the brain was applied as a masking region of interest

(ROI) to each normalized PET scan image to obtain the time-activity curves (Lee et al., 2005). Time-activity curves of putamen, caudate nucleus, occipital lobe, hippocampal formation, thalamus, cingulate cortex, and cerebellum were used for the kinetic analysis (Huang et al., 2002).

Compartmental analysis

For the selection of best model to describe the kinetics of [^{11}C]sertraline, two tissue compartment model with reversible receptor-ligand biding [Tc2_k1234] and its nested models (two tissue compartment model with irreversible binding [Tc2_k123] and single tissue compartment model [Tc1_k12]) were compared in terms of the AIC values (Fig. 2). In Fig. 2, C_a is arterial plasma concentration, C_f is free or non-specifically bound tracer concentration, and C_b is specifically bound tracer concentration. In single tissue compartment model, C_T is the concentration in tissue compartment where the free or non-specific and specific bindings cannot be distinguished.

Kinetic parameters (K_1, k_2, k_3, and k_4) are the rate constants describing the mass transfer between the compartments. K_1, k_2, k_3, and k_4 are defined as the delivery (mL/min/g), washout (min^{-1}), forward receptor-ligand reaction (min^{-1}), and reverse receptor-ligand reaction (min^{-1}), respectively.

To obtain the kinetic parameters, the Levenberg-Marquardt method was adapted for non-linear curve fitting. The initial parameter values were fixed with 0.9 for K_1, 0.001 for k_2, and 0.01 for k_3 and k_4. Time-activity curves between 0-90 min were used for the curve fitting.

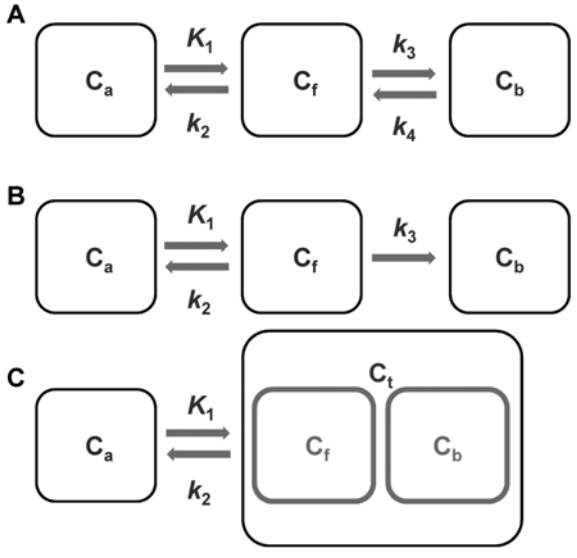

Fig. 2. Three expectable compartment models for [^{11}C]sertraline. (**A**) is 2 tissue compartment reversible model [Tc2_k1234], (**B**) is 2 tissue compartment irreversible model [Tc2_k123], (**C**) is single tissue compartment model [Tc1_k12].

Model selection

Akaike information criteria (AIC) was used as criterion for the selection of the best model (Ludden et al., 1994):

$$\mathrm{AIC} = N \ln SS + 2P$$

, where N is number of data points on tissue time-activity curves, SS sum of square obtained by the curve fitting, and P number of unknown parameters.

Comparison of quantitative parameters

For the single tissue compartment model, total distribution volume (DV=K_1/k_2) for each ROI and DV ratio (DVR) between each ROI and reference region (cerebellum) were calculated. In addition, ratio between the standard uptake value (SUV) of each region and that of cerebellum (SUVr) was computed using the following equation, and the correlation analysis between SUVr and DVR was performed (Lopresti et al., 2005).

$$SUV_r = \frac{\int_{50\ \mathrm{min}}^{90\ \mathrm{min}} C_T(t)dt}{\int_{50\ \mathrm{min}}^{90\ \mathrm{min}} C_{cerebellum}(t)dt}$$

RESULTS

Blood analysis

Sampled blood was consist of 63% blood cell, 36% protein and 1% supernatant. It showed small changes during the first 30 min (2, 4, 8, 15, 30 min). At the end time point of our study, 30 min, blood cell decreased to 55%, protein increased to 38% and supernatant increased to 7% of the total blood amount.

Time activity curves

Fig. 3 shows typical time-activity curves for the putamen, caudate nucleus, occipital cortex, hippocampal formation, thalamus, cingulate, and cerebellum, and arterial plasma input function. The activity in plasma dropped rapidly after injection. As the time-activity curves at the brain regions reach plateau after about 50 min with high retention, it seems that this tracer bounds to the binding sites irreversibly within the PET scan time.

Model selection

We attempted to fit the data to each of the three models. In all model fittings, the RMSE (root mean square error) was between 1.026 and 3.150. Parameter

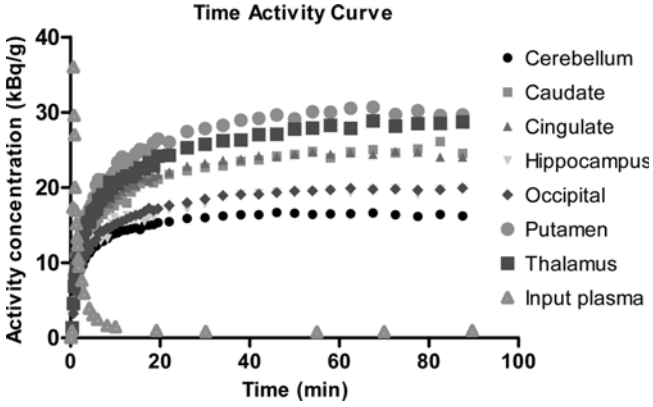

Fig. 3. Representative time-activity-curves in 7 brain regions (cerebellum, caudate, cingulate, hippocampus, occipital, putamen and thalamus) and input in a volunteer.

values estimated using each model are shown in Table I.

In the putamen, the average K_1 was 0.54 mL/min/g in each of Tc1_k12 and Tc2_k123 models, and 0.5 mL/min/gin Tc1_k1234. The average k_2 was 0.12 min^{-1} in all models. All models yielded similar values of K_1/k_2 as k_3 and k_4 were negligibly small in 2 tissue compartment models. Fig. 4 shows the fitting curves for putamen in a subject using these three different models, indicating that there is no difference in the quality of curve fitting.

In all of the studies, single tissue compartment with a two-parameter model had a lower AIC (Ludden et al., 1994) than the two-tissue compartment models with three or four parameters (Table II) in all ROI regions

Table I. Results of kinetic analysis by using different models in the putamen region during 90 min

Model	Volunteer#	K_1	k_2	K_1/k_2	k_3	k_4	RMSE
Tc1_k12	#1	0.42	0.008	51.38	-	-	1.68
	#2	0.48	0.013	37.16	-	-	1.18
	#3	0.44	0.010	45.01	-	-	1.05
	#4	0.42	0.010	40.33	-	-	1.34
	#5	0.95	0.020	48.25	-	-	3.13
	Average	0.54	0.012	44.42	-	-	1.84
Tc2_k123	#1	0.42	0.008	49.70	0.00017	-	1.71
	#2	0.49	0.014	35.76	0.00087	-	1.23
	#3	0.43	0.009	46.31	0.00011	-	1.05
	#4	0.42	0.011	39.46	0.00082	-	1.37
	#5	0.94	0.020	47.29	0.00004	-	3.20
	Average	0.54	0.012	43.70	0.00040	-	1.71
Tc2_k1234	#1	0.35	0.007	49.99	0.002	0.001	1.47
	#2	0.48	0.013	35.82	0.001	0.003	1.23
	#3	0.41	0.010	40.50	0.002	0.001	1.03
	#4	0.34	0.010	34.41	0.004	0.001	1.16
	#5	0.91	0.020	45.47	0.001	0.001	3.15
	Average	0.50	0.012	41.24	0.002	0.001	1.61

Tc1_k12 is single tissue compartment model, Tc2_k123 is two tissue irreversible compartment model, Tc2_k1234 is two tissue reversible compartment model.

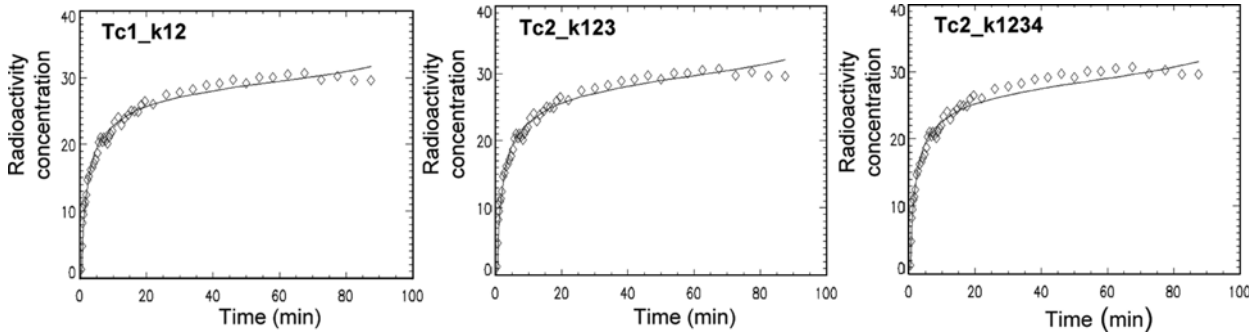

Fig. 4. Kinetic model comparison among the three expected models. Nonlinear fitting to the measured data using PET scan.

Table II. Akaike information criteria (AIC) analysis in ROI regions

Regions of interest	AIC in Model 1	AIC in Model 2	AIC in Model 3
Putamen	25.90 ± 21.93	27.50 ± 21.83	29.53 ± 21.82
Cerebellum	14.33 ± 27.59	15.93 ± 27.36	17.72 ± 27.32
Caudate	17.75 ± 29.53	19.35 ± 29.30	21.33 ± 29.29
Cingulate	22.05 ± 21.04	23.65 ± 20.81	25.58 ± 20.80
Hippocampus	13.99 ± 21.07	15.59 ± 20.83	17.20 ± 20.69
Occipital	4.26 ± 24.44	5.86 ± 24.17	8.00 ± 24.25
Thalamus	19.93 ± 26.88	21.53 ± 26.57	23.52 ± 26.57

*Mode 1: Tc1_k12, Model 2: Tc2_k123, Model 3: Tc2_k1234. AIC, Akaike Information Criteria

Table III. Estimated kinetic parameters (average K_1, k_2, DV and DVR-1) in ROI during 90 min

Region	Average		DV	DVR-1
	K_1 (mL/min/g)	k_2 (1/min)	K_1/k_2	
Putamen	0.54	0.01	42.3	0.68
Cerebellum	0.43	0.02	25.1	-
Caudate	0.43	0.01	32.7	0.3
Cingulate	0.45	0.01	32.4	0.29
Hippocampus	0.35	0.01	26.9	0.07
Occipital	0.36	0.01	25.7	0.02
Thalamus	0.48	0.01	37.2	0.48

(putamen, cingulate, caudate, hippocampus, occipital white matter, thalamus and cerebellum), confirming that K_1 and k_2 are sufficient to describe the kinetics of this tracer (Table I). As a result, the simpler model, the single tissue compartment model, was the optimal fit model to describe the TAC.

Kinetic parameter estimation and comparison

K_1, k_2 and their ratio (DV) for each ROI is summarized in Table I. Putamen and thalamus showed high DV values, caudate and cingulate showed intermediate DV values, and cerebellum, occipital and hippocampal formation showed low DV values (Table III). This result is concordant with the known density of serotonin transporter (SERT) (Huang et al., 2002).

Fig. 5 shows the distribution of estimated DV values according to the scan time for parameter estimation (Boecker et al., 2005). Although most subjects showed relatively consistent DV values, one subject showed much overestimated DV values before 40 min.

Fig. 6 shows the results of correlation analysis between SUVr and DVR, which shows the good correlation between them. This indicates that the SUVr with the integration of scan time of 50-90 min can be a simplified quantitative parameter reflecting the DVR of this tracer (r = 0.98, SUVr = 0.76 DVR + 0.18).

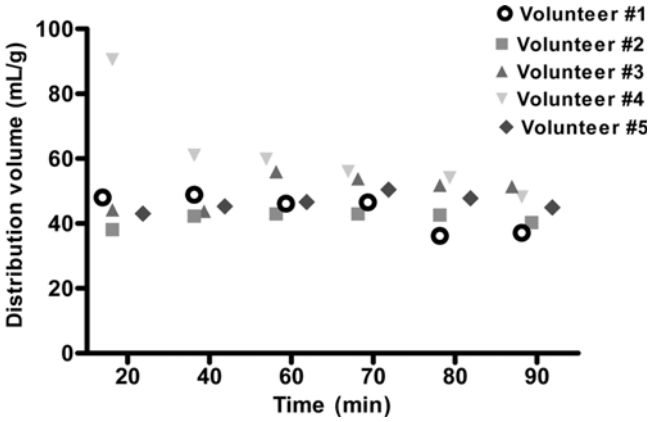

Fig. 5. Distribution volume (DV) changes according to different PET scan time duration.

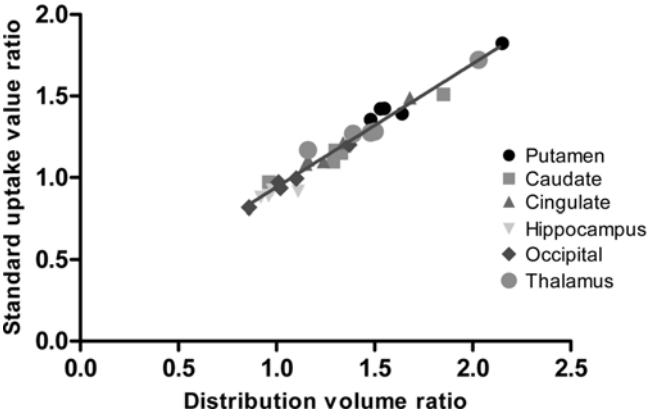

Fig. 6. Correlation between standard uptake value ratio (SUVr) during 50 to 90 min and distribution volume ratio (DVR).

DISCUSSION

In recent days, receptor imaging gets great interest in many clinical fields and is widely used as a dosing drug study for the psychological-pharmaceutical field (Huang et al., 2002; Frankle et al., 2004). Preliminary studies in our animal study in two micro pigs, we found out that the bio-distribution of [^{11}C]sertraline matches well with the known density of serotonin receptors in the brain. To study of widely using SSRI drug, sertraline, investigating it's kinetic movement is important for extending it's application (Szabo et al., 1999). By using a PET, which is sensitive detector to study the images of the [^{11}C]sertraline with micro dose (< 12.8 nmol of sertraline).

In this study, we conducted a first trial to make a kinetic model with [^{11}C]sertraline in healthy human brain. As the tracer consists of sertraline itself and

radionuclide, we could obtain more practical results than using other tracers.

We observed during a 90-120 min PET scanning and fused with MRI, but there was no significant clearance after tissue uptake at the time activity curve. Rapid uptake occurred in the brain means that sertraline easily penetrating the brain blood barrier (BBB). Also, the flat time activity curves in the ROI during long time indicated the drug's high binding potential in the serotonin receptor or trapped situation in the target region. In addition, it is possible that metabolite of the radio tracer was competitively stick to the binding site with the active radio tracer. Although the supernatant of the tracer at the first 30 min was under 10%, the amountis not an ignorable value at 90 min after injection. Metabolism of the tracer cannot obtain exactly as it's short half-life and small amount, but it may possibly affect the result.

In this study, based on the Akaike Information Criteria (AIC), the most suitable compartment model is Tc1_k12 with 2 parameters (e.g., radioligand uptake in tissue K_1 and radioligand release from tissue k_2). Long sustaining curve indicated that high affinity which is relate with influx rate K_1 and low deflux rate k_2 rather than k_3 and k_4. Also the total fitting quality among the compartment models did not show a big difference. As a result, the simplest model was chosen for explaining the kinetic properties of sertraline.

None of these kinetic parameters are correlated with the serotonin density. However, the radioactivity concenration ratio, especially total Distribution Volume (DV) demonstrated in Table II showed correlation with the density of serotonin receptor (Huang et al., 2002). As DV is more constant and stable value than micro kinetic parameters K_1, k_2. The result shows that the total Distribution Volume (DV) can be the representative kinetic parameter of [^{11}C]sertraline.

Also, the DV change according to scan time indicates that minimum scan time should be 50 min for adequate kinetic study for [^{11}C]sertraline. Although the number of volunteer was small in this study, the tendency of DV change was visible.

DV can only obtained by blood sampling which make volunteers hard to endure. As the result, we verified the semi-quantitative method SUVr which use a reference region cerebellum in tissue. As cerebellum contains the lowest serotonin receptors, it is widely used for reference region of specific binding (Szabo et al., 1999; Frankle et al., 2004). High correlation between SUVr and DVR showed that SUVr can replace DV in the further kinetic study of [^{11}C]sertraline without blood sampling for the image analysis.

In conclusions, comparing with different parameter numbers in compartment modeling with radiotracer [^{11}C]sertraline, the single tissue compartment model (Tc1_k12) with two parameter K_1 and k_2 was chosen as the best fitting kinetic model for sertraline, and can explain the movement of sertraline *in vivo*. We found out the drug's high uptake and sustaining in the brain tissue.

Also, dynamic PET scan time longer than 50 min should be required for the accurate estimation of Distribution Volume ($DV = K_1/k_2$) of [^{11}C]sertraline in healthy human brain. In addition, SUVr (50-90 min) which is more convenient method than DVR was proved as the feasible simplified quantitative parameter reflecting the DVR of this tracer.

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