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Time-course of serotonin transporter occupancy by single dose of three SSRIs in human brain: A positron emission tomography study with [^{11}C]DASB

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ABSTRACT

Sixteen healthy volunteers were enrolled and divided into four groups according to the single administration of 10 mg or 20 mg escitalopram, 50 mg sertraline, or 20 mg paroxetine. Four positron emission tomography scans with [^{11}C]DASB were performed on each subject, the first prior to taking the drug, followed by the others at 4, 24, and 48 h after. Serotonin transporter occupancies of the drugs at each time point were calculated. All drugs showed maximum occupancy at 4 h after dosing and then decreasing occupancies with time. Escitalopram and sertraline showed high occupancies of 69.1–77.9% at 4 h, remaining at 52.8–57.8% after 48 h. On the other hand, paroxetine showed relatively low occupancy of 44.6%, then decreasing to 10.3% at 48 h. Escitalopram (both 10 mg and 20 mg) and sertraline (50 mg) showed high and sustained occupancy. Paroxetine (20 mg) showed relatively low and rapidly decreasing occupancy, possibly due to the low plasma concentration by single dosing schedule. Applying the reported concentration of multiple dosing, 20 mg paroxetine will induce over 80% occupancy. The present study suggested that these drugs and doses would be sufficient for the treatment of depression.

1. Introduction

Selective serotonin reuptake inhibitors (SSRI) are recommended by some clinical guidelines for the treatment of depression (APA, 2010; NICE, 2009). Their main mechanism of action is thought to be the blockade of serotonin transporter (SERT) in the synaptic cleft. Several SSRIs have been investigated for their SERT occupancy, meaning the magnitude of blockade to target molecules, by positron emission tomography (PET) using radioligands such as [^{11}C]DASB and [^{11}C]MADAM, which have high affinity and selectivity for SERT (Ginovart et al., 2001; Ichise et al., 2003; Lundberg et al., 2005). Meyer et al. reported that four SSRIs and venlafaxine showed more than 80% SERT occupancy in patients treated for depression (Meyer et al., 2001; Meyer et al., 2004). Other studies also suggested that the clinical dose of SSRIs blocked around 80% SERT (Lundberg et al., 2007; Parsey et al., 2006; Suhara et al., 2003; Voineskos et al., 2007). The time-course of drug action is also important in respect to the usage or regimen of antidepressant treatment; e.g. how many times the drug should be administered. Some studies reported the discrepancy about the time-course between plasma concentration and occupancy in the brain (Abanades et al., 2011; Takano et al., 2006a, 2006b). Together with the threshold of the effectiveness of SSRIs, the time-course of SERT occupancy as measured by PET is useful for estimating the pharmacodynamics of antidepressants.

In Japan, the first SSRI, fluvoxamine, became available in 1999, and the latest one, escitalopram, in 2011. Now, we are able to use four SSRIs (fluvoxamine, paroxetine, sertraline, and escitalopram) and two serotonin norepinephrine reuptake inhibitors (SNRIs; milnacipran, duloxetine). The time-courses of SERT occupancy by duloxetine and fluvoxamine were investigated in a Japanese population (Takano et al., 2006a, 2006b). However, the other SSRIs have not yet been estimated in Japan. Evaluation of the time-course of SERT occupancy in a Japanese population will be important because the difference of effectiveness by SSRI treatment between Asians and Caucasians has been reported (Porcelli et al., 2012). In this study, we investigated the time-course of SERT occupancy by the single administration of three SSRIs, escitalopram, sertraline, and paroxetine, over the same measurement schedule using PET and [^{11}C]DASB to assess the pharmacodynamics of these

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drugs.

2. Methods

2.1. Subjects

Sixteen healthy volunteers (age range, 20–35 years; mean ± SD, 29.1 ± 4.6; eight males, eight females) were enrolled in the study. None had a history of present or past psychiatric, neurological or somatic disorders, or alcohol or drug-related problems. All subjects were non-smokers. After thorough explanation of the study, written informed consent was obtained from all participants. This study was approved by the ethics committee of the institutional review board of Nippon Medical School Hospital, Tokyo, Japan and was accomplished in compliance with the latest revision (2008) of the Declaration of Helsinki.

2.2. Study design

This study was designed as a single-administration, open-label protocol using three drugs. The subjects were divided into four groups of four subjects each: 10 mg or 20 mg escitalopram, 50 mg sertraline, and 20 mg paroxetine. Four PET scans were performed on each subject, the first prior to taking the drugs, followed by three more at 4 (around the peak of drug concentration), 24, and 48 h after. Due to the failure of radioligand preparation, two subjects in the 20 mg escitalopram group were measured as baseline scan three weeks after drug administration.

2.3. PET procedures

PET scans were carried out with Eminence SET-3000GCT-X (Shimadzu Corp., Kyoto, Japan) to measure regional brain radioactivity. This scanner provides 99 sections with an axial field of view (FOV) of 26.0 cm. The spatial resolution was 3.45 mm in-plane and 3.72 mm axially full-width at half maximum (FWHM). A head fixation device was used during the scans. A 4-min transmission scan was done to correct for attenuation using a ^{137}Cs source. Dynamic PET scan was performed for 90 minutes (1 min × 4, 2 min × 13, 4 min × 5, 8 min × 5) after intravenous bolus injection of [^{11}C]DASB. Injected radioactivity was 313.4–392.4 MBq (367.3 ± 13.2 MBq). Specific radioactivity was 14.1–103.5 GBq/μmol (36.8 ± 15.0 GBq/μmol) at the time of injection.

2.4. MRI procedures

Magnetic resonance (MR) images of the brain were acquired with 1.5 T MR imaging, Intera 1.5 T Achieve Nova (Philips Medical Systems, Best, Netherlands). T1-weighted MR images were obtained at 1-mm slices.

2.5. Measurement of plasma concentration of drugs

Venous blood samples were taken just before each PET scan, collected in tubes containing EDTA-2Na, and centrifuged at 3000 rpm for 10 min at 4 °C. Separated plasma samples were stored at −80 °C until analysis. Plasma concentration was measured by a validated method using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a target lower quantification limit of 0.1 ng/mL (Sumika Chemical Analysis Service, Osaka, Japan).

2.6. Data analysis

All MR images were co-registered to summated PET images with the mutual information algorithm using PMOD (version 3.4; PMOD Technologies Ltd, Zurich, Switzerland). Regions of interest (ROIs) defined for the thalamus and cerebellar cortex were drawn manually on overlaid summated PET and co-registered MR images of each scan. The average values of right and left ROIs were used for the analysis. Regional radioactivity was calculated for each frame, corrected for decay and plotted vs. time. Motion correction by matching the targeted frame to the previous one was conducted in three scans of two subjects due to head motion.

SERT binding of [^{11}C]DASB was quantified using a simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996). The cerebellum was used as reference region because of its low SERT density (Kish et al., 2005). This model allows the estimation of binding potential (BP_{ND}), which was defined as $f_{ND} \times B_{avail}/K_d$, where f_{ND} is the free fraction of ligand in the non-displaceable tissue compartment, B_{avail} is the transporter density, and K_d is the dissociation constant (Innis et al., 2007).

SERT occupancy by drugs was calculated by the following equation:

$$\text{Occupancy } (\%) = (BP_{base} - BP_{drug}) / BP_{base} \times 100.$$

Occupancy is SERT occupancy, BP_{base} is BP_{ND} under drug-free condition, and BP_{drug} is BP_{ND} under drug-taking condition (Takano et al., 2006a, 2006b). SERT occupancies of each time point by the 4 drug groups were calculated.

The relationship between plasma concentration and SERT occupancy was shown by the following equation:

$$\text{Occupancy } (\%) = C/(EC_{50}+C) \times 100$$

C is the plasma concentration of the drug and EC_{50} is the plasma concentration required to achieve 50% occupancy (Takano et al., 2006a, 2006b). Maximum occupancy is assumed as 100%. Correlations between plasma concentration and SERT occupancy were examined.

3. Results

All sixteen subjects completed the four scans and did not complain of any symptoms such as nausea or drowsiness.

The plasma concentrations and SERT occupancies by 10 mg escitalopram, 20 mg escitalopram, 50 mg sertraline and 20 mg

Table 1
Drug concentration and SERT occupancy by 4 drug groups with time.

		Drug concentration (ng/mL)			SERT occupancy (%)		
		4 h	24 h	48 h	4 h	24 h	48 h
Escitalopram	10 mg	13.8 (2.3)	6.5 (1.8)	3.2 (1.2)	69.1 (6.7)	65.7 (6.0)	52.8 (10.8)
Escitalopram	20 mg	25.3 (6.9)	11.3 (3.5)	4.9 (2.1)	77.9 (3.4)	71.5 (5.0)	57.8 (11.8)
Sertraline	50 mg	19.4 (6.1)	8.3 (1.5)	3.8 (0.9)	74.3 (5.6)	69.3 (4.5)	56.6 (6.6)
Paroxetine	20 mg	4.8 (5.1)	1.8 (2.4)	0.4 (0.5)	44.6 (21.1)	31.7 (28.1)	10.3 (20.6)

*Drug concentration and SERT occupancy are represented by 'mean (SD)'.