TABLE 1
Estimated Rate Constants for 3 Methods

Region	2-input NLS			1-input NLS (60 min)			1-input NLS (15 min)			Integration plot	
	K_1	k_2	BV	K_1	k_2	BV	K_1	k_2	BV	K_1	BV
Frontal	0.047	0.071	0.052	0.044	0.047	0.055	0.047	0.069	0.052	0.043	0.062
	(16.9)	(11.2)	(9.06)	(16.9)	(10.6)	(9.17)	(16.8)	(11.0)	(8.80)	(15.6)	(16.5)
Temporal	0.046	0.068	0.058	0.043	0.044	0.060	0.046	0.064	0.057	0.043	0.067
	(16.2)	(9.97)	(12.2)	(16.4)	(10.2)	(12.1)	(16.2)	(11.1)	(12.3)	(12.5)	(21.9)
Parietal	0.049	0.073	0.055	0.045	0.047	0.058	0.049	0.068	0.056	0.044	0.068
	(17.0)	(10.6)	(9.58)	(17.0)	(11.3)	(9.60)	(17.1)	(13.1)	(9.31)	(14.1)	(19.2)
Occipital	0.050	0.068	0.072	0.046	0.047	0.073	0.048	0.062	0.071	0.046	0.073
	(15.4)	(17.2)	(16.2)	(16.5)	(11.7)	(15.7)	(16.5)	(15.2)	(16.2)	(13.7)	(27.3)
Cerebellum	0.049	0.077	0.059	0.045	0.051	0.062	0.049	0.074	0.059	0.044	0.070
	(15.3)	(10.2)	(10.5)	(15.2)	(11.2)	(10.1)	(15.3)	(9.04)	(10.5)	(11.4)	(22.9)

2-input NLS: K_1, k_2, and BV values estimated by NLS with 2-input, 2-tissue compartment model for measured data up to 60 min; 1-input NLS: K_1, k_2, and BV values estimated by NLS with 1-input, 1-tissue compartment model for measured data up to 60 or 15 min; Integration plot: K_1 and BV values estimated by graphical analysis with integration plot. Mean with COV in parentheses; mean value and normalized percent SD of each parameter for 10 subjects.

result consistent with that of Sasongko et al. (*18*). The measured time–activity curve was well described with the 2-input, 2-tissue compartment model, including the passing of the main metabolite in plasma to the brain (Fig. 3). Although the good fit of the 2-input compartment model does not represent evidence for the existence of metabolites permeating the BBB, this result suggests the possibility of the contribution of metabolites to the measured activity.

Graphical Analysis

In Equation 2, the term of BV is not included. The plots with this equation were not on the straight line even in early-time data. The value of K_1 was small in the ^{11}C-verapamil study, so the effect of BV cannot be neglected. Therefore, we modified Equation 2 to Equation 4, and the estimated BV value was valid.

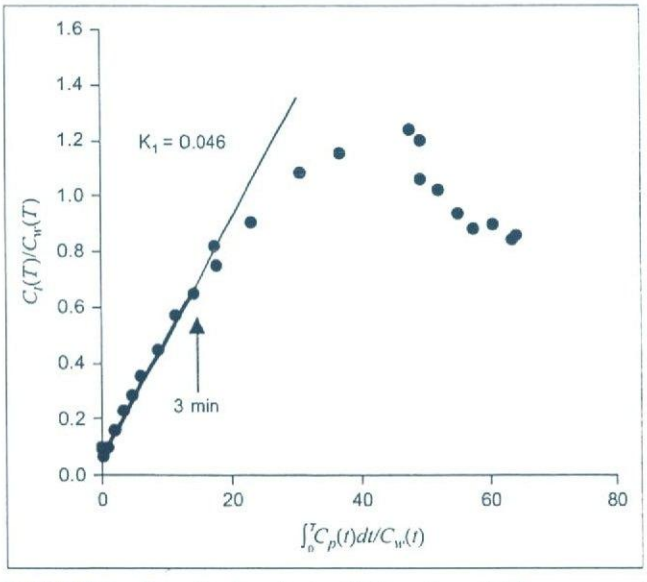

FIGURE 4. Graphical analysis of integration plot for measured time–activity curve of temporal cortex. K_1 value was estimated by using points between 15 s and 3 min.

Even if the metabolites in plasma pass the BBB, the K_1 value estimated by the integration plot is not affected by them because the integration plot yields K_1 from only early-time data, in which the plasma fraction of the unchanged form is >95%. Therefore, estimation by the integration plot does not require consideration of the effect of the metabolites, which becomes a problem in NLS with the compartment model or the graphical analysis of Logan et al. (*15*). Although the integration plot provides only K_1, and more detailed quantification such as NLS with the compartment model is necessary to understand the overall dynamics of the tracer, it is useful in the evaluation of the difference in K_1 between subjects.

However, by this method, K_1 was underestimated (Fig. 5C). This underestimation may be a result of neglecting the efflux from the brain, represented as k_2. Actually, the integration plot of Equation 4 contains only the time during which the efflux from the brain did not appear. When k_2 is small, the effect of the efflux is negligible for a few minutes after the injection. However, when k_2 is larger, the efflux cannot be negligible even for only a few minutes after the injection (Fig. 6). In the simulation study, the error of underestimation was greatly affected by the k_2 value, indicating that the integration plot is not appropriate for a tracer with large k_2 and regional or individual large variations of k_2. In healthy volunteers, K_1 estimated by the 2-input compartment model ranged from 0.046 to 0.050, k_2 ranged from 0.068 to 0.077, and DV ranged from 0.64 to 0.74 (Table 1), indicating that regional differences of these parameters are small. Moreover, the COV of k_2 and the DV among individuals were about 10% in all regions. In these variations of k_2 and DV among regions and individuals, the

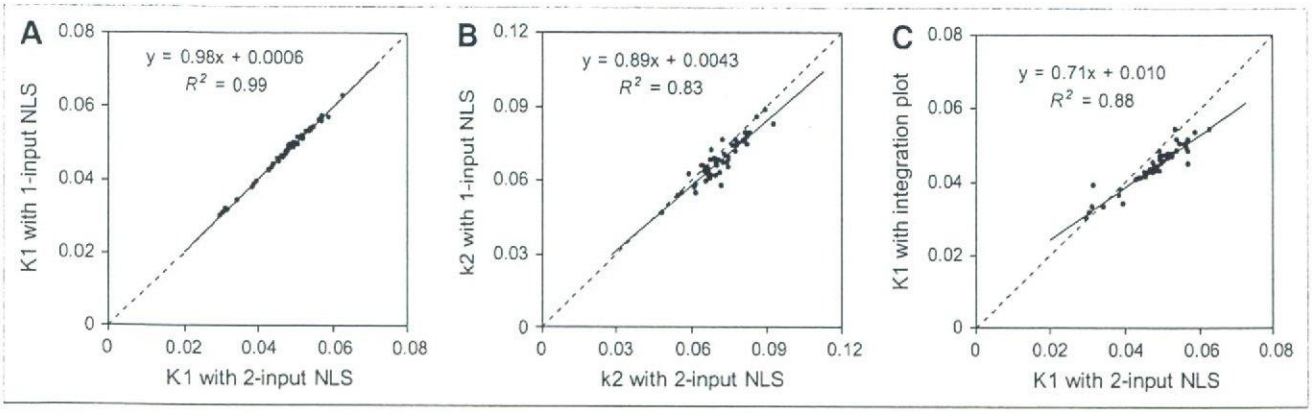

FIGURE 5. Relationship between K_1 estimated from NLS with 1-input compartment model for 15-min measured data and that with 2-input compartment model for 60-min data (A), between k_2 estimated from NLS with 1-input compartment model for 15-min measured data and that with 2-input compartment model for 60-min data (B), and between K_1 estimated from integration plot and that from NLS with 2-input compartment model for 60-min measured data (C).

difference of K_1 underestimation resulting from the k_2 and DV is small. The underestimation of estimated K_1 in this DV value was about 10% when K_1 was estimated by using points up to 3 min (Fig. 6). In the future, ^{11}C-verapamil will be applied for various diseases and, in a case with a large k_2, interpretation of the estimated K_1 should be attempted with caution.

Considering the effect of the efflux across the BBB, the endpoint of linear regression should be selected as early as possible. However, too early an endpoint of linear regression brings about an estimation error caused by statistical noise in the tissue time–activity curve, especially in the time–activity curve with a high noise level. Deducing from the residual error of time–activity curve fitting by NLS, the noise level of human ROI analysis in this study was 1%–3% (*31*). At this noise level, the COV of graphical analysis is small enough. However, in pixel-by-pixel calculation, the noise level is large. In a time–activity curve with 20% noise at the 16th frame (mean time point = 10 min), the COV of K_1 by graphical analysis with data up to 3 min was >35%, this was larger than that by NLS with 1-input compartment model. When the endpoint for linear regression was >5 min, the COV became smaller than NLS with the 1-input compartment model. However, bias of the underestimation became larger as the endpoint became later. Therefore, graphical analysis is not appropriate for pixel-by-pixel calculation.

NLS with Compartment Model

The 2-input compartment model can provide the rate constants of transfer of metabolite between plasma and brain, and the radioactivity of metabolite in brain. However, the COV of K_1^M and k_2^M were >50%, so estimated parameters without constraint are not reliable.

NLS with the 1-input compartment model can provide K_1 with data from only 15 min, in which the rate of unchanged verapamil in plasma is about 80%. Therefore, the 1-tissue compartment model is also useful for the estimation of transfer from plasma to brain, K_1. However, k_2 cannot be estimated reliably in a short-time scan and would be greatly affected by metabolites in brain if they exist. More studies focusing on metabolites in the brain will be necessary for the evaluation of k_2.

Indicator of P-gp Function in ^{11}C-Verapamil Studies

The integration plot does not require consideration of the permeation of BBB for the metabolites. However, the integration plot provides only K_1. Nevertheless, Muzi et al. reported that increase in K_1 estimates in the presence of CsA in

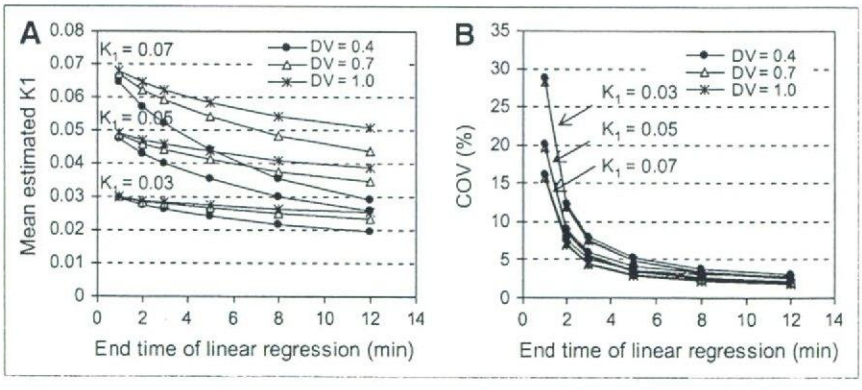

FIGURE 6. Relationship between mean estimated K_1 of integration plot and end time of linear regression (A) and between COV of estimated K_1 and end time of linear regression (B) for simulated time–activity curves with noise levels of 3% with K_1 = 0.03, 0.05, and 0.07, and DV = 0.4, 0.7, and 1.0.

healthy volunteers was independent of blood flow and demonstrated inhibition of P-gp efflux at the BBB (*21*). Moreover, Lee et al. reported that the transfer of ^{11}C-verapamil evaluated by the integration plot increased after treatment with P-gp inhibitor, PSC833, in nonhuman primates (*20*). Therefore, taken together, the estimation of K_1 is deemed to be helpful for the assessment of P-gp function in the BBB.

CONCLUSION

The rate constant of transfer to the brain, K_1, was estimated by graphical analysis of an integration plot with data points of an initial few minutes, during which the rate of unchanged verapamil in radioactivity of plasma is >95%. In human data with healthy volunteers, K_1 estimated by graphical analysis correlated with that by NLS with the 2- or 1-input compartment model. In the simulation study, the COV of K_1 by graphical analysis was smaller than that by other methods in the noise level of ROI analysis. The integration plot is useful for the estimation of transfer to the brain, as this method can provide K_1 easily with only the data of the initial few minutes without needing to consider the permeability of metabolite in plasma.

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ARTICLE

The antipsychotic sultopride is overdosed – a PET study of drug-induced receptor occupancy in comparison with sulpiride

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Abstract

Conventional antipsychotics tend to elicit extrapyramidal symptoms at clinical doses, but dose optimization could reduce the risk of such side-effects. In-vivo receptor-binding studies have suggested that 70–80% of dopamine D_2 receptor occupancy provides the desired antipsychotic effects without extrapyramidal symptoms. In terms of dose optimization based on the occupancy, there has not been enough supporting data regarding the clinical doses of the respective antipsychotics. In this study, we measured dopamine D_2 receptor occupancy of two conventional benzamide antipsychotics, sulpiride and sultopride, using positron emission tomography, to investigate the rationale of their clinical dose. Although they are prescribed at similar doses (300–1200 mg), the doses required to obtain similar receptor occupancy (70–80%) were quite different: 1010–1730 mg for sulpiride but 20–35 mg for sultopride. In terms of dose, sultopride has about 50 times greater potency than sulpiride based on dopamine D_2 receptor occupancy. Evidence for the optimal doses of conventional antipsychotics based on dopamine D_2 receptor occupancy would be helpful for rational antipsychotic therapy.

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Key words: Antipsychotics, dopamine D_2 receptor, dose settings, occupancy, PET.

Introduction

Conventional antipsychotics have been regarded as drugs with more frequent extrapyramidal side-effects (EPS) compared with second-generation antipsychotics (Gerlach and Peacock, 1995; Waddington et al., 1997). However, a recent meta-analysis suggested that low-potency conventional antipsychotics at optimal doses might in fact not induce more EPS than second-generation antipsychotics (Leucht et al., 2003), and another meta-analysis reported that second-generation antipsychotics were found not to have greater efficacy than high-potency conventional antipsychotics at lower dose (Geddes et al., 2000). Discussion on the scientific evidence for clinical doses of conventional antipsychotics has been inconclusive, and opposing results were also reported in a meta-analysis (Davis et al., 2003). Although antipsychotics are classified in several ways, in the present article, the term 'second-generation antipsychotics' refers to clozapine and all the novel antipsychotics introduced in the 1990s, and 'conventional antipsychotics' refer to older antipsychotics. The advent of positron emission tomography (PET) has made it possible to measure the receptor occupancy of antipsychotics in the living human brain (Farde et al., 1988). PET studies have suggested that a range of 70–80% of dopamine D_2 receptor occupancy provides the desired antipsychotic effects without EPS (Farde et al., 1992; Kapur et al., 2000). It was also suggested that one advantage of the use of second-generation

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antipsychotics might be better explained by the determination of appropriate clinical dose settings (Kapur and Mamo, 2003). Amisulpiride, a benzamide antipsychotic drug, was reported to show fewer EPS and has been regarded as a second-generation antipsychotic drug; its clinical doses were reported to show appropriate dopamine D_2 receptor occupancy (Martinot et al., 1996). On the other hand, sulpiride and sultopride, other benzamide antipsychotics, were considered as conventional antipsychotics. Despite their similar registered clinical doses (sulpiride 300–600 mg, max 1200 mg; sultopride 300–600 mg, max 1800 mg in Japan) and the fact that the equivalency of clinical potency was reported (2 mg haloperidol is equivalent to 200 mg sulpiride or 200 mg sultopride) (Inagaki et al., 1999), sultopride has been reported to induce more EPS than sulpiride (Peselow and Stanley, 1982). The relationship between the dose/plasma concentration and dopamine D_2 receptor occupancy by the two drugs has not been fully explored. Since they are relatively selective dopamine D_2 receptor antagonists (Peselow and Stanley, 1982), their dopamine D_2 receptor occupancy in the living human brain can be expected to provide us with the criteria to decide the appropriate doses. In this study we measured dopamine D_2 receptor occupancy of the two conventional substitute benzamide antipsychotics, sulpiride and sultopride, to investigate the rationale for their dose settings.

Materials and methods

Subjects

Twenty-one male healthy volunteers (26.6 ± 5.7 yr) were enrolled in this study. None had a history of psychiatric or neurological illness, chronic somatic illness or substance abuse. None was receiving any medication, and none had a close relative with a known psychiatric illness.

After description of the study, written informed consent was obtained from all subjects. This study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences, Chiba, Japan.

Radioligand

The precursors of [^{11}C]FLB 457 were kindly supplied by Astra Arcus (Sodertaje, Sweden). [^{11}C]FLB 457 was synthesized by *O*-methylation of the corresponding precursors with [^{11}C]methyliodide with high specific radioactivity, which was obtained by a reduction of [^{11}C]CO_2 with $LiAlH_4$ in an inert atmosphere with specially designed equipment (Halldin et al., 1995; Suzuki et al., 1999). The radiochemical purities were more than 95%.

PET procedure

Dynamic scans were performed for 90 min using ECAT EXACT HR+ (CTI-Siemens, Knoxville, TN, USA) immediately after a bolus injection of 220 ± 16 MBq of [^{11}C]FLB 457 with high specific radioactivities (141 ± 34 GBq/μmol).

MRIs were acquired on Gyroscan NT (Philips Medical System, Best, The Netherlands) (1.5 T) to obtain T1-weighted images of the brain.

Two PET scans were performed, one before antipsychotics administration, and the second at the possible peak time of plasma concentration of the drugs, 3 h after a single dose of sulpiride (200–800 mg; 3 subjects at 200 mg, 3 at 400 mg, 3 at 600 mg, 2 at 800 mg) and 2 h after a single dose of sultopride (10–200 mg; 3 subjects at 10 mg, 3 at 25 mg, 2 at 50 mg, 1 at 100 mg, 1 at 200 mg). Three subjects with sultopride (50, 100, and 200 mg respectively) did not complete the 90-min PET scans due to akathisia and EPS, with PET data of 60 min being used for the subject receiving 200 mg and 70 min for the two subjects receiving 50 mg and 100 mg sultopride respectively. Blood samples were taken just before each PET scan for concentration measurements of sulpiride or sultopride.

The subjects were examined for EPS, akathisia, and other adverse effects after the PET scans by two psychiatrists who were aware of the dosage of the antipsychotics.

Data analysis

All emission scans were reconstructed with a Hanning filter cut-off of 0.4. Regions of interest (ROIs) (prefrontal cortex, temporal cortex, thalamus, cerebellum) were drawn on PET/MRI images by a template-based method (Yasuno et al., 2002). The average values of right and left ROIs were used to increase the signal-to-noise ratio for the calculations. Quantification of PET data was performed using a three-parameter simplified reference tissue model to estimate binding potential (BP) (Lammertsma and Hume, 1996). The cerebellum was used as the reference tissue because of its negligible density of dopamine D_2 receptors for calculation (Suhara et al., 1999). This model allows the estimation of BP, which was defined as the ratio of receptor density (B_{max}) to dissociation constant (K_d). Dopamine D_2 receptor

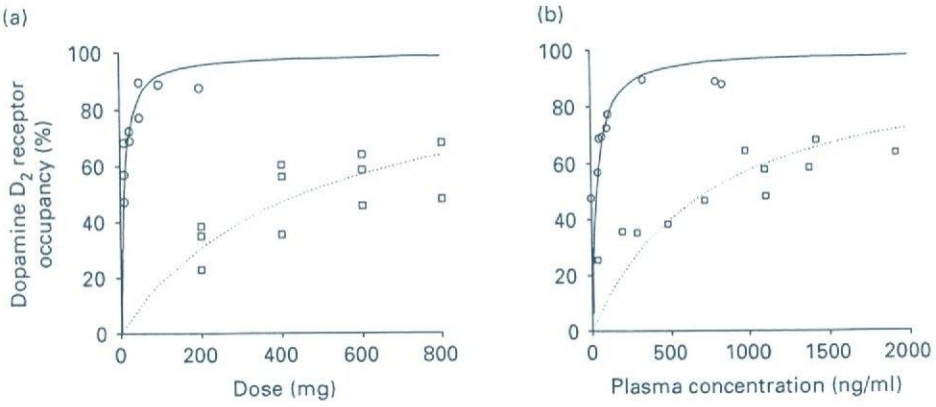

Figure 1. Relationship between dopamine D_2 receptor occupancy and doses of sulpiride and sultopride (a), and between dopamine D_2 receptor occupancy and plasma concentrations of sulpiride and sultopride (b). Mean dopamine D_2 receptor occupancy of three regions (prefrontal cortex, temporal cortex, and thalamus) was shown as dopamine D_2 receptor occupancy. Open squares indicate sulpiride, and open circles indicate sultopride. The dotted regression curve was fitted to the sulpiride data, and the solid regression curve was fitted to the sultopride data.

occupancy by antipsychotics was calculated using the following equation:

$$Occu = (BP_{baseline} - BP_{drug}) \times 100/BP_{baseline},$$

where Occu is receptor occupancy, $BP_{baseline}$ is BP in the drug-free state, and BP_{drug} is BP of the subject on the drug.

The relationship between dopamine D_2 receptor occupancy and dose/plasma concentration of antipsychotics was fitted to the following equation:

$$D_{2,occu} = 100 \times D/(ED_{50} + D),$$

where $D_{2,occu}$ is dopamine D_2 receptor occupancy, ED_{50} is the dose/concentration to induce 50% occupancy, and D is the dose/concentration of the drug (Fitzgerald et al., 2000; Kapur and Remington, 1996).

The measurement of plasma concentrations of sulpiride and sultopride

The plasma concentration of sulpiride was measured according to a previous report (Tokunaga et al., 1997) with the following modification. The HPLC column was a Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 10% CH_3CN in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

The plasma concentration of sultopride was measured according to a previous report (Kobari et al., 1985) with the following modification. The HPLC column was Waters Xterra RP18, a 150 × 3.9 mm i.d. with a mobile phase of 12% CH_3CN in 0.1 M phosphate buffer (pH 2.0) at a flow rate of 1.0 ml/min. A UV detector was set at 235 nm.

Results

The mean dopamine D_2 receptor occupancy in the three regions (prefrontal cortex, temporal cortex, and thalamus) ranged from 25.3% to 68.3% on doses of 200–800 mg sulpiride and from 47.4% to 89.4% on doses of 10–200 mg sultopride. Occupancy values of the three subjects taking sultopride and not completing the 90-min PET scans due to EPS or akathisia were more than 87%. No subjects taking sulpiride showed akathisia or EPS. None of the 21 subjects showed any other adverse effects. For both sulpiride and sultopride, mean dopamine D_2 receptor occupancy increased as the dose and plasma concentration increased (Figure 1a,b). There were no obvious differences in occupancy among the three regions. The S.D. of dopamine D_2 receptor occupancy among the three regions ranged from 0.9% to 10.2% (mean ± S.D., 5.1 ± 3.0%) for sulpiride and from 0.8% to 6.5% (4.3 ± 1.9%) for sultopride. The ED_{50} value of sulpiride was 433 mg ($r = 0.69$) for dose and 740 ng/ml ($r = 0.71$) for plasma concentration, while that of sultopride was 8.7 mg ($r = 0.85$) for dose and 32 ng/ml ($r = 0.66$) for plasma concentration.

Discussion

Despite the similar registered clinical doses for sulpiride and sultopride (Inagaki et al., 1999), the ED_{50} values measured by PET were quite different. Based

on the dopamine D_2 receptor occupancy, sultopride has approx. 20 times greater potency than sulpiride when viewing plasma concentration, and approx. 50 times greater potency in terms of dose. Calculating the optimal doses with this occupancy data, 1010–1730 mg sulpiride would be required to obtain 70–80% of dopamine D_2 receptor occupancy, while 20–35 mg sultopride would be sufficient. The calculated optimal dose range for sulpiride overlapped with the upper range of the registered clinical doses. On the other hand, the registered clinical doses of sultopride were approx. 10 times higher than the calculated optimal doses. Clinically, sultopride has been used for sedation rather than for the treatment of psychotic symptoms, and it was reported to have a high incidence of EPS (Peselow and Stanley, 1982). However, the present results suggest that a much lower dose of sultopride would be sufficient to treat psychotic symptoms. A future clinical trial would be required with such lower dose.

There are some pharmacological differences in the profiles of the two drugs. The affinity to dopamine D_2 receptor of sultopride (IC_{50} value 18 nM) was higher than that of sulpiride (69 nM) (Mizuchi et al., 1982). In addition, the brain uptake from blood was much higher for sultopride compared to sulpiride (Mizuchi et al., 1983). As the log p value was 1.46 for sultopride and 0.42 for sulpiride, the difference in brain uptake was considered to be due to the higher lipophilicity of sultopride (Mizuchi et al., 1983). Since drug transport is regulated by efflux transporters such as P-glycoprotein at the blood–brain barrier (Wang et al., 2004), we investigated the possibility of a *substrate* of P-glycoprotein for both drugs. However, we could not obtain supportive data for any *substrate* (data not shown). The different receptor occupancy profiles of the two drugs could be attributed to differences in drug affinity and penetration into the brain.

Despite the pharmacological differences, the clinical doses of the two drugs were determined as equivalent (Inagaki et al., 1999). Several potential problems concerning the process of determining the clinical doses of antipsychotics at the stages of both animal and clinical studies seem to exist. In a series of animal experiments, the inhibition of apomorphine- or methamphetamine-induced stereotyped behaviour and the induction of catalepsy were evaluated for sulpiride and sultopride (Araki et al., 1986). In the inhibition of apomorphine-induced stereotyped behaviour, sultopride was approx. 100 times weaker than haloperidol. For catalepsy induction, sultopride was approx. 25 times weaker than haloperidol (Araki et al., 1986). Although a series of paradigms such as the inhibition of apomorphine- and methamphetamine-induced stereotyped behaviours was used for animal studies, psychiatric symptoms in human patients could not themselves be modelled as in animals. The optimal dose in any such model will certainly not represent the dose for humans, making it difficult to estimate optimal doses for humans from animal experiments. Doses chosen on the basis of an animal study were often unrepresentative of the clinical condition (Kapur et al., 2003), and the doses in a clinical study tended to be higher than the minimum optimal dose (Talvik et al., 2004). In clinical studies, several preliminary reports were published in the 1970s regarding the use of sultopride in psychiatric disorders (Genevieve and Couriol, 1976; Maurel and Pujol, 1975; Robert, 1978). However, the doses in those reports were diverse, from 200 mg to 4800 mg, and a variety of patients were included (Peselow and Stanley, 1982). In a double-blind comparative study of sultopride (800–1600 mg) with thioproperazine (8–16 mg), EPS emerged for both drugs, and no differences in EPS were reported between them (Sizaret and Moreau, 1977). In a double-blind comparative study of sultopride with haloperidol, the dose (300–1800 mg/d) was defined on the basis of an animal study, a phase-two study and preliminary clinical data (Kudo et al., 1987). In that study, antiparkinsonian medications were allowed to be prescribed, and it was concluded that sultopride was as efficacious as haloperidol. However, the co-administration with antiparkinsonian medications might have masked any possible overdose. In another double-blind study for comparison between sulpiride (300–1800 mg) and sultopride (300–1800 mg), antiparkinsonian medications were also allowed (Kudo et al., 1986), and the effectiveness of the two drugs was judged to be not significantly different. Again, EPS might have been masked by the antiparkinsonian medications. In clinical studies for antipsychotics, symptoms and side-effects of patients with schizophrenia would not be easy to evaluate if also using antiparkinsonian medications.

Since the clinical doses of amisulpride were reported to show appropriate dopamine D_2 receptor occupancy (Martinot et al., 1996), one advantage of the use of second-generation antipsychotics might be better explained by the application of appropriate clinical dose settings.

Although sulpiride was introduced in the clinical field in the 1970s and is classified as a conventional antipsychotic (Ago et al., 2005; Keltner and Johnson, 2002), some reports considered it as an 'atypical' antipsychotic due to its low EPS rate (Caley and Weber, 1995; Rummel et al., 2003). The present result

indicated that the clinical doses of sulpiride overlapped with the lower range of the optimal doses. If the proper setting of the clinical dose explains the low rate of EPS, sulpiride could be regarded as 'atypical'.

There are several confounding factors in this study. First, we measured occupancy with normal subjects after a single administration. Although it is unlikely that there is a marked difference in dopamine D_2 receptor occupancy between normal subjects and patients with schizophrenia, further occupancy studies in patients with schizophrenia and repeated administrations may provide useful information. Second, although most previous occupancy reports were based on striatal measurements, we measured extrastriatal regions with [^{11}C]FLB 457 because limbic and cortical regions were suggested to be a site of antipsychotic actions (Lidow et al., 1998; Pilowsky et al., 1997). The test–retest reproducibility was good, with a mean variability of 4.5% for the thalamus, 7.7% for the frontal cortex, and 5.4% for the temporal cortex (Sudo et al., 2001). Although the regional differences of dopamine D_2 receptor occupancy by clozapine was reported (Pilowsky et al., 1997), there have been discussions on the methodology (Olsson and Farde, 2001) and similar occupancy values of antipsychotics were obtained in extrastriatal regions and the striatum in several studies (Nyberg et al., 1999, 2002; Takano et al., 2004; Talvik et al., 2001; Vernaleken et al., 2004; Yasuno et al., 2001). Thus, the threshold of dopamine D_2 receptor occupancy in the striatum was also considered to be applicable to extrastriatal regions. Third, 3 out of the 21 volunteers did not complete the 90-min PET scans, and their results were based on 60–70 min data. Nevertheless, the time to reach equilibrium was within 60 min in those regions, and a simplified reference tissue method has been reported to produce reliable BP for over 60 min (Olsson and Farde, 2001).

In summary, despite the similar registered clinical doses for sulpiride and sultopride, based on dopamine D_2 receptor occupancy, sultopride has ~50 times greater potency than sulpiride. As evidence for the clinical doses of conventional antipsychotics has been limited, their re-evaluation based on dopamine D_2 receptor occupancy is warranted for the establishment of rational antipsychotic therapy.

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Statement of Interest

None.

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