Pharmacokinetics and time-course of D$_2$ receptor occupancy induced by atypical antipsychotics in stabilized schizophrenic patients

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Abstract

The $^{123}$I-IBZM SPECT measured D$_2$ receptor occupancy ($D_2$RO) in chronically dosed, stabilized schizophrenic patients and its relationship with antipsychotic (AP) pharmacokinetics (PK) over time is still unclear. The aims of this study were: 1) To define the relationship between striatal D$_2$ receptor occupancy ($D_2$RO) and plasma concentration ($C_P$) in stabilized schizophrenic patients on clinically relevant doses using $^{123}$I-IBZM SPECT; 2) To investigate the time course of AP-induced $D_2$RO and corresponding $C_P$. Forty-six schizophrenic patients on their clinically required doses of risperidone, olanzapine, clozapine or quetiapine were included. $D_2$RO and $C_P$ were measured over time following a sparse-sampling experimental design, and individual PK and $D_2$RO-time profiles were estimated using a population approach. Observed striatal $D_2$RO and $C_P$ ranges were 28–75% and 9.4–60.5 ng/mL for risperidone, 22–84% and 8.6–89.5 ng/mL for olanzapine, 5–53% and 41.6–818.2 ng/mL for clozapine and 0–64% and 37.9–719.6 ng/mL for quetiapine. A PK–$D_2$RO relationship was found for the four APs. $D_2$RO pattern over time was stable for risperidone, olanzapine and clozapine but fluctuating for quetiapine. Stabilized schizophrenic patients show a wide range of both $D_2$RO and $C_P$ at clinically effective doses of the four AP, suggesting that clinical response to these AP may be maintained with $D_2$RO below 65%. $D_2$RO patterns over time differ between AP. These results should be considered for accurate interpretation of $D_2$RO measurements, proper design of studies and optimization of drug regimens for patients on AP treatment.

Keywords schizophrenia, D$_2$ receptor, PK-PD model, atypical, antipsychotics, SPECT

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Introduction

It has been claimed that antipsychotic drugs (AP) exert their action by means of blockade of D₂ receptors (Seeman et al., 1976). Positron emission tomography (PET) and single photon emission computed tomography (SPECT) allow the in vivo assessment of AP-induced D₂ receptor occupancy (D₂RO) (Nyberg et al., 1995; Kufferle et al., 1997; Dresel et al., 1998; Gefvert et al., 1998; Kapur et al., 1999; Tauscher et al., 1999). However, despite extensive literature on this subject, the degree of D₂RO associated to the PK–D₂RO relationship using SPECT for risperidone (Knable et al., 1999), olanzapine (Kapur et al., 1999), clozapine (Perry et al., 2000) and quetiapine (PK–D₂RO relationship). Moreover, knowledge of the influence of the scanning time within the interdose interval could be relevant for an adequate interpretation of D₂RO measurements. Any relationship between brain and plasma kinetics could be of value for dosing schedules.

In this study, a sparse-sample experimental design and population modelling approach were used with the following aims: first, to define the relationship between striatal D₂RO measured by ¹²³I-BZM SPECT and Cₚ in stabilized schizophrenic patients on risperidone, olanzapine, clozapine and quetiapine (PK–D₂RO relationship). Second, to evaluate the time-course of the D₂RO profile, and third, to compare the profiles of D₂RO and Cₚ over time for these AP.

Methods and materials

Subjects

Demographic and clinical characteristics of the patient population are summarized in Table 1. A total of 46 patients (32 male, 29.5 ± 6.5 years) with DSM-IV-TR diagnosis of schizophrenia, schizoaffective or schizoaffective disorders were included in the study. Thirty-six of the included patients met the criteria for schizophrenia (86% paranoid, 8% undifferentiated, 3% disorganized and 3% residual subtypes), seven for schizoaffective disorder and three for schizoaffective disorder. All patients were required to be responding to AP medication, defined as scoring ≤65 on the Positive and Negative Syndrome Scale (PANSS) (Kay, 1987) and scoring ≤4 on the Clinical Global Impression Scale (CGI) (Guy, 1976). Severity of extrapyramidal symptoms (EPS) was assessed at inclusion by means of the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard, 1980). The subgroups of patients for each AP did not differ by age (F = 1.49, df = 3, P = 0.23), length of illness (F = 0.19, df = 3, P = 0.90), PANSS score (F = 0.58, df = 3, P = 0.63), CGI score (F = 0.50, df = 3, P = 0.69), or ESRS score (F = 0.47, df = 3, P = 0.70). All patients had been on monotherapy for at least two months with one of the following AP at clinically required doses: risperidone (n = 12; 1.5–7 mg/day), olanzapine (n = 12; 5–30 mg/day), clozapine (n = 12; 50–600 mg/day) and quetiapine (n = 10; 200–800 mg/day). EPS were absent or very mild in all cases. All patients had normal physical examination, 12-lead electrocardiogram, clinical chemistry and hematology findings. Pregnancy was excluded in females by means of a urine pregnancy test (Clearview HCG II; Unipath Limited). Patients had abstained from taking any adjunctive medication apart from the prescribed
PK, and the individual D2RO time course. Each group of patients empirical Bayesian approach was used to estimate the individual population data to estimate the average time-course. Then an only one tracer injection and was scanned once due to dosimetry strategy permits to properly characterize the entire D2RO time-course in the population of the individuals evaluated accounting for which a limited number of samples are collected in each subject. This design was used. A sparse sampling design is a study design in which a limited number of samples are collected in each subject.

AP 14 days prior to the SPECT examination, except for contraceptives or benzodiazepines with a maximum dose equivalent to 3 mg lorazepam. Only three patients on risperidone and two on quetiapine received benzodiazepines. None of the patients had received any depot AP in the year before, and none was taking anticholinergics for drug-induced EPS. Smoking was allowed up to 20 cigarettes per day. Absence of illegal drugs of abuse was assessed by a urine drug screening (InstaCheck Drug Screen Test, Applied Biotech/Forefront Diagnostics, San Diego, USA). None had concurrent substance abuse or dependence (with the exception of nicotine).

The study was approved by the Ethics Committees from all the participating centres and the Spanish Ministry of Health, and written informed consent was obtained in all cases prior to inclusion in the study.

Study design

An open-labelled, randomized, parallel group, sparse-sample design was used. A sparse sampling design is a study design in which a limited number of samples are collected in each subject and where the sampling times differ from subject-to-subject. This strategy permits to properly characterize the entire D2RO time-course in the population of the individuals evaluated accounting for the independent contribution of each subject. Each patient received only one tracer injection and was scanned once due to dosimetry limitations. A non-linear mixed effects modelling was applied to the population data to estimate the average time-course. Then an empirical Bayesian approach was used to estimate the individual PK, and the individual D2RO time course. Each group of patients on each treatment regimen were subdivided in four subgroups of n = 2–3 and allocated randomly to undergo the SPECT scan at one time point during the interdose interval, defined based on known PK for each AP, that is the time of maximum AP C_p (T_max); before T_max (pre-T_max); at T_max; early after-T_max and late after-T_max (Tables 2 and 4). Blood samples were drawn during SPECT scanning for AP plasma levels measurement (see Plasma Analysis section).

\(^{123}\)I-IBZM SPECT imaging procedure

SPECT was performed using a Prism 3000S camera (Philips Medical Systems, The Netherlands) fitted with ultrahigh-resolution fanbeam collimators. Subject preparation included administration of potassium perchlorate (5 mg/kg) before \(^{123}\)I-IBZM injection to minimize radiation exposure to the thyroid. Four SPECT/MRI markers, each filled with 0.054 MBq of \(^{123}\)I and olive oil, were stuck on the mastoids and the corners of the eyes. \(^{123}\)I-IBZM (Amersham Health/Cygne, 185.2 ± 13.3 MBq) was injected intravenously flushed with saline. A 30-min scan was acquired starting 90 min after radioligand injection. Each frame was collected using a 360° circular orbit, step and shoot mode every 3°, matrix 128 × 128 pixels. A venous catheter for blood sampling was inserted on the arm opposite to the radioligand injection in all subjects.

All subjects underwent a T-1 weighted 3D MRI scan for coregistration and region of interest (ROI) drawing. A superconductive 1.9 Tesla system (Prestige T, General Electric) equipped with a head coil was used. Images were acquired with the following parameters: repetition time, 25 ms; echo time, 6 ms; flip angle, 28°; field of view, 25 × 25 cm; matrix size, 256 × 256; section thickness, 2 mm with no interslice gap; and number of excitations, 1.

Image processing

Images were reconstructed using a filtered-backprojection algorithm with a Butterworth filter (exponent = 5.0; cutoff frequency = 0.4

<table>
<thead>
<tr>
<th>AP Group</th>
<th>Dose (mg/day)</th>
<th>n</th>
<th>Age</th>
<th>Gender</th>
<th>DSM-IV-TR Diagnosis (n)</th>
<th>Illness length (years)</th>
<th>Treatment length (years)</th>
<th>PANSS</th>
<th>CGI</th>
<th>ESRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>4.8 ± 1.8</td>
<td>12</td>
<td>28.3 ± 4.2</td>
<td>10M, 2F</td>
<td>S.p.(12)</td>
<td>5.2 ± 3.2</td>
<td>2.5 ± 2.0</td>
<td>42.9 ± 7.5</td>
<td>2.1 ± 0.7</td>
<td>3.4 ± 2.5</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>12.9 ± 6.8</td>
<td>12</td>
<td>28.2 ± 7.2</td>
<td>7M, 5F</td>
<td>S.p.(8); Sph.D.(2); S.d.(1); S.r.(1)</td>
<td>5.3 ± 4.2</td>
<td>2.2 ± 1.6</td>
<td>45.6 ± 7.0</td>
<td>2.4 ± 0.7</td>
<td>4.0 ± 2.5</td>
</tr>
<tr>
<td>Clozapine</td>
<td>304.2 ± 180.2</td>
<td>12</td>
<td>29.4 ± 6.5</td>
<td>10M, 2F</td>
<td>S.p.(5); Sph.D.(3); Sa.D.(2); S.u.(2)</td>
<td>6.7 ± 4.7</td>
<td>4.2 ± 3.3</td>
<td>46.3 ± 10.7</td>
<td>2.1 ± 0.8</td>
<td>2.7 ± 3.8</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600.0 ± 235.7</td>
<td>10</td>
<td>32.8 ± 7.7</td>
<td>5M, 5F</td>
<td>S.p.(6); Sph.D.(2); S.d.(1); S.u.(1)</td>
<td>6.5 ± 8.9</td>
<td>1.3 ± 1.0</td>
<td>42.3 ± 8.2</td>
<td>2.1 ± 1.0</td>
<td>3.0 ± 2.3</td>
</tr>
<tr>
<td>Total</td>
<td>~</td>
<td>46</td>
<td>29.5 ± 6.5</td>
<td>32M, 14F</td>
<td>S.p.(31); Sph.D.(7); Sa.D.(3); S.u.(3); S.d.(1); S.r.(1)</td>
<td>5.9 ± 5.4</td>
<td>2.6 ± 2.4</td>
<td>44.4 ± 8.4</td>
<td>2.2 ± 0.8</td>
<td>3.3 ± 2.8</td>
</tr>
</tbody>
</table>

All values expressed as mean ± standard deviation; n: number of patients; M: male; F: female; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders revised version; PANSS: Positive and Negative Syndrome Scale; CGI: Clinical Global Impression; ESRS: Extrapyramidal Symptoms Rating Scale. For DSM-IV-TR Diagnosis, values represent classification (number of patients in each class between brackets), according to: S.p.: Schizophrenia paranoid type; S.d.: Schizophrenia disorganised type; S.r.: Schizophrenia residual type; S.u.: Schizophrenia undifferentiated type; Sph.D.: Schizophreniform disorder; Sa.D.: Schizoaffective disorder.
cycle/pixel). Attenuation correction was performed using Chang’s algorithm (\(\mu = 0.1 \text{cm}^{-1}\)). SPECT and MRI scans were registered using external markers manually identified on the MRI and SPECT scans. A rigid body transformation was estimated automatically by minimizing the sum of squared distances between the corresponding marker positions. Striatum and occipital cortex ROI were manually drawn on the MRI.

### Data analysis

The tissue ratio method was used for quantification. The specific to non-specific partition coefficient, representing the ratio of specific binding in the target region to non-specific binding in the reference region was measured by means of specific uptake ratios (SUR) from each subject as \(\text{SUR} = [(S-O)/O]\), where S and O were the average counts in the striatum and occipital cortex, respectively. Individual \(D_{2\text{RO}}\) values were directly calculated from the experimental data as \(D_{2\text{RO}}^{\text{observed}} = 100 \cdot ([0.95-\text{SUR}_{\text{AP}}]/0.95)\), where \(\text{SUR}_{\text{AP}}\) is the SUR obtained in patients on medication and 0.95 the mean SUR value from a group of healthy volunteers previously studied (\(n = 28, 23\) M, 26.2 ± 5.1 years, Catafau et al., 2005), who did not differ in age with the patients included in the present study (\(F = 1.51, df = 4, P = 0.21\)). These \(D_{2\text{RO}}^{\text{observed}}\) were the pharmacodynamic (PD) input for the PK–PD analysis. PK/D\(D_{2\text{RO}}\) modelling approaches were used to evaluate the relationship between \(C_p\) of each AP and their respective brain-induced \(D_{2\text{RO}}\).

### PK–PD analysis

Three PK samples were drawn from each patient across the SPECT procedure 30 min apart. Population-PK (Pop-PK) modelling was undertaken using non-linear mixed-effect modelling as implemented in NONMEM (version V) to assess population PK of the four AP tested. Inter-subject variability and residual error were also assessed. Empirical Bayesian methods were used to estimate individual PK parameters. For risperidone-treated patients the \(C_p\) reported and modelled was the active moiety (risperidone plus its active metabolite 9-hydroxy-risperidone).

It has been shown that it is possible to obtain unbiased estimates of population model parameters using sparse sampling when prior information on drug PK are used in the data-modelling procedure (Ette and Williams, 2004). Using this approach, the \(C_P\)s of each APs were analyzed by fixing the population estimates of volume of distribution (Vd), absorption rate constant (\(k_a\)) and their inter-individual variability to the population values reported in the literature (Huang et al., 1993 for risperidone; Callaghan et al., 1999 for olanzapine; Jirling et al., 1997 for clozapine and Kimko et al., 2000 for quetiapine). In all cases the time course of drug \(C_p\) was modelled using a one-compartment open model with first-order absorption and elimination assuming steady state dosing. The following prior information was included in the Pop-PK: for risperidone, the non-compartmental PK parameters (area under the curve AUC, plasma half-life \(T_{1/2}\) and \(T_{\text{max}}\)) reported by Huang et al. (1993) were used to extrapolate the compartmental parameters Vd, clearance (CL) and \(k_d\). For olanzapine, PK values reported by Callaghan et al. (1999) for average and standard deviation for CL and Vd were used. Average \(k_a\) was selected in order to reproduce the \(T_{\text{max}}\) reported. For clozapine and quetiapine, the reported Pop-PK values (Jirling et al., 1997; Kimko et al., 2000) were used.

PK/D\(D_{2\text{RO}}\) modelling approaches were based on a direct link model between \(C_p\) and \(D_{2\text{RO}}\). The relationships between AP \(C_p\) and \(D_{2\text{RO}}\) were assessed using sigmoidal \(E_{\text{max}}\) model:

\[
D_{2\text{RO}}^{\text{cp}} = \frac{D_{2\text{RO}}^{\text{max}}}{\text{EC}_{50} + C_p^{\gamma}} \cdot C_p
\]

where \(C_p\) was the average AP plasma concentration during the SPECT scan, \(D_{2\text{RO}}^{\text{max}}\) the theoretical maximum displacement for the particular AP, \(\text{EC}_{50}\) the \(C_p\) associated with 50% of the maximum displacement, and \(\gamma\) the slope factor. After a preliminary PK–PD assessment it was decided to fix the slope factor to 1 for all the AP except quetiapine, for which visual inspection of the PK–D\(D_{2\text{RO}}\) relationship suggested a sharper transition between \(C_p\) associated with approximately zero \(D_{2\text{RO}}\) and levels associated with moderate (around 50%) \(D_{2\text{RO}}\). Given the sparse sampling strategy adopted, it was possible to estimate inter-subject variability only for the potency parameter (\(\text{EC}_{50}\)). The measurement error was fixed as additive with a standard deviation of 7% \(D_{2\text{RO}}\), which is half of the estimated test-retest variability studied in healthy subjects (Catafau et al., 2008).

### Table 2

Reported PK parameters and SPECT scan time selection after last dose intake for each AP

<table>
<thead>
<tr>
<th>AP Group</th>
<th>Dose regimen</th>
<th>Reported PK parameters</th>
<th>SPECT scan time after last AP dose intake (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(T_{\text{max}})</td>
<td>(T_{1/2})</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>once/day</td>
<td>1.5</td>
<td>22</td>
</tr>
<tr>
<td>Clozapine</td>
<td>twice/day</td>
<td>2.1</td>
<td>12</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>twice/day</td>
<td>1.5</td>
<td>6</td>
</tr>
</tbody>
</table>

*Risperidone active moiety, i.e. risperidone + 9-OH-risperidone.

AP: antipsychotic; \(T_{\text{max}}\): time of maximum plasma concentration; \(T_{1/2}\): mean plasma half-life.
PK and D\textsubscript{2}RO profiles over time were compared. Using the PK–PD model parameters, simulated D\textsubscript{2}RO curves (D\textsubscript{2}RO\textsubscript{Sim}) were generated for a single representative dose for each AP, that is 6 mg/day for risperidone; 15 mg/day for olanzapine; 450 mg/day for clozapine and 650 mg/day for quetiapine.

**Plasma analysis**

Risperidone, 9-hydroxy-risperidone, olanzapine, clozapine and quetiapine C\textsubscript{p} was measured at 90, 105 and 120 min after radioligand injection, using a validated solid phase extraction – liquid chromatography – mass spectrometry/mass spectrometry method (Dear et al., 1998) by SAS analytics (Stoneleigh Deer Park, Stareton, Kenilworth, Warks). Limits of quantification were 5 ng/mL for risperidone and 9-hydroxy-risperidone, 1 ng/mL for olanzapine, 20 ng/mL for clozapine and 15 ng/mL for quetiapine.

**Statistical analysis**

Statistical analyses were implemented using SPSS v.12.0 (SPSS Inc., Chicago, Ill.). Factorial ANOVA was used to compare demographic and clinical characteristics at inclusion among groups. A probability value of 0.05 was selected as significance level.

**Results**

**PK analysis**

In two patients, one on risperidone 3 mg/day and one on quetiapine 200 mg/day, the C\textsubscript{p} were found to be below the limit of quantification. These two patients were not included in the PK and PK–PD datasets. Observed C\textsubscript{p} ranges were: risperidone 9.4–60.5 ng/mL; olanzapine 8.6–89.5 ng/mL; clozapine 41.6–818.2 ng/mL and quetiapine 37.9–719.6 ng/mL.

Pop-PK parameters, together with their inter-subject variability (CV\%) for each AP are shown in Table 3.

**PK–PD analysis**

Striatal D\textsubscript{2}RO ranged from 28% to 75% for risperidone, 22–84% for olanzapine, 5–53% for clozapine and 0–64% for quetiapine. Individual D\textsubscript{2}RO values and corresponding C\textsubscript{p} and time of scan after last dose administration for each patient are presented in Table 4. Model predicted D\textsubscript{2}RO\textsubscript{Sim} as a function of C\textsubscript{p} are shown in Figure 1, and Pop-PK–PD parameters for each AP are shown in Table 5. PK–D\textsubscript{2}RO curves for risperidone, olanzapine and clozapine were hyperbolic with γ = 1, whereas for quetiapine was sigmoidal, with γ = 3. In agreement with the corresponding affinities for the D\textsubscript{2} receptor, risperidone and olanzapine showed higher potency at the D\textsubscript{2} receptor, that is required lower C\textsubscript{p} to occupy 50% of the available D\textsubscript{2} receptors (EC\textsubscript{50}) than clozapine and quetiapine. Moreover, risperidone and olanzapine showed similar EC\textsubscript{50} whereas quetiapine showed approximately double EC\textsubscript{50} than clozapine (Table 5). Risperidone showed moderate variability in estimated potency (individual EC\textsubscript{50} from 8.3 to 42.8 ng/mL) and population PK–D\textsubscript{2}RO predictions were in good agreement with observed data (r\textsuperscript{2} = 0.60). Olanzapine showed low inter-subject variability in potency (individual EC\textsubscript{50} from 17.2 to 26.1 ng/mL) and population model predictions were in very good agreement with observed data (r\textsuperscript{2} = 0.97). Clozapine showed lower estimated D\textsubscript{2}RO\textsubscript{max} than risperidone and olanzapine (Table 5); high inter-subject variability in potency (EC\textsubscript{50} ranging from 59 to 1418 ng/mL) and population PK–D\textsubscript{2}RO predictions were not in good agreement with the observed data (r\textsuperscript{2} = 0.10). Quetiapine showed slightly higher estimated D\textsubscript{2}RO\textsubscript{max} than clozapine but lower than risperidone and olanzapine (Table 5); inter-subject variability in potency was moderate (EC\textsubscript{50} ranging from 386 to 856 ng/mL) and the population PK–D\textsubscript{2}RO predictions were in good agreement with the observed data (r\textsuperscript{2} = 0.60).

Co-registered MRI/SPECT images from two representative patients on each AP treatment at T\textsubscript{max} and late after T\textsubscript{max} are shown in Figure 2. D\textsubscript{2}RO\textsubscript{Sim} patterns over time for risperidone, olanzapine and clozapine showed a maintained D\textsubscript{2}RO, ranging between 45 and 68% for risperidone 6 mg/day, 53–61% for olanzapine 15 mg/day and 32–43% for clozapine 450 mg/day. These were dissociated from the PK profile over time. However, D\textsubscript{2}RO\textsubscript{Sim} patterns over time matched the corresponding PK curves for quetiapine at all doses (Figure 3). Mean maximum D\textsubscript{2}RO\textsubscript{Sim} at peak quetiapine C\textsubscript{p} was 45% at 650 mg/day, with D\textsubscript{2}RO reaching 0% during the dosing interval.

**Discussion**

**PK analysis**

A wide range of C\textsubscript{p} was observed at therapeutic doses of risperidone, olanzapine, clozapine and quetiapine in clinically stabilized schizophrenic patients, consistent with reports of high interindividual PK variability for these AP (Huang et al., 1993; Byerly et al., 1996; Darby et al., 1997; Kimko et al., 2000; Harvey et al., 2001; Raggi et al., 2004; Hiemke et al., 2004).

Population parameters for the four APs and their inter-subject variability were in good agreement with published data for risperidone (Huang et al., 1993; Byerly et al., 1996; Darby et al., 1997; Burns, 2001), olanzapine (Jerling et al., 1997; Callaghan et al., 1999; Burns, 2001; Chiu et al., 2004; Sidhu et al., 2006), clozapine (Byerly et al., 1996; Guitton et al., 1998; Burns, 2001) and quetiapine (Gefvert et al., 1998; Kimko et al., 2000; DeVane and Nemeroff,
Table 4 Individual D2RO values, \( C_p \), and scan time after last dose administration

<table>
<thead>
<tr>
<th>Risperidone</th>
<th>Olanzapine</th>
<th>Clozapine</th>
<th>Quetiapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient number</td>
<td>( C_p ) (ng/mL)</td>
<td>Scan time (h)*</td>
<td>D2RO (%)</td>
</tr>
<tr>
<td>1</td>
<td>60.5</td>
<td>22</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>34.2</td>
<td>0.5</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>23.2</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>58.0</td>
<td>1.5</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>14.3</td>
<td>1.5</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>45.1</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>38.6</td>
<td>0.5</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>32.6</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>9.4</td>
<td>0.5</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>53.7</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>14.2</td>
<td>22</td>
<td>42</td>
</tr>
</tbody>
</table>

The two patients with \( C_p \) below limits of quantification are not included (see text). \( C_p \): Plasma concentration; D2RO: D2 receptor occupancy. *Hours after last antipsychotic dose administration.
PK/PD model for atypical antipsychotics using SPECT

between 10–60 ng/mL for risperidone (Darby et al., 1997; Olesen et al., 1998; Mauri et al., 2001; Hiemke et al., 2004; Raggi et al., 2004), 8–80 ng/mL for olanzapine (Olesen and Linnet, 1999; Perry et al., 2001; Fellows et al., 2003; Raggi et al., 2004; Hiemke et al., 2004) and between 350 and 600 ng/mL for clozapine (Perry et al., 1991; Miller et al., 1994; Raggi et al., 2004; Hiemke et al., 2004).

For quetiapine, plasma concentrations ranging between 50 and 400 ng/mL have been suggested by Raggi et al. (2004) to be associated with clinical efficacy. In the present sample of stabilized schizophrenic patients, 75% of the patients on risperidone and olanzapine, but only 25% on clozapine and 30% on quetiapine showed CP within these suggested ranges. For clozapine, this may be explained because some patients were responding to low doses. For quetiapine, the reference range could be strongly influenced by the PK sampling time since the PK and the associated D2RO peak to trough fluctuations may be highly variable due to its short half-life.

PK–PD analysis

A wide range of D2RO was observed at therapeutic doses of risperidone, olanzapine, clozapine and quetiapine in clinically stabilized...
schizophrenic patients. Risperidone and olanzapine showed similar PK–D₂RO profiles both in terms of D₂RO_{MAX} and EC_{50} (Figure 1), suggesting that D₂RO-equivalent C_p of risperidone and olanzapine could be in the ratio of 1:1 ng/mL, as previously reported by Kapur et al. (1999). C_p inducing D₂RO = 50% for risperidone (26.9 ng/mL) and olanzapine (22.7 ng/mL) are within the reported therapeutic C_p ranges for these AP, suggesting that 123I-IBZM SPECT measured D₂RO around 50% may be enough for clinical efficacy. Moreover, less than 25% on risperidone and olanzapine and none on clozapine or quetiapine showed D₂RO above 65%, value claimed as a lower threshold for AP efficacy for haloperidol-treated patients with first-episode schizophrenia by means of 11C-Raclopride PET (Kapur et al., 2000). According to the PK–D₂RO relationships found in the present study, the C_p needed to reach 65% D₂RO for olanzapine (42.2 ng/mL) is higher than the C_p observed in 10 out of 12 patients, and for risperidone (53.7 ng/mL) is close to the highest observed C_p value (Figure 1). At least for risperidone and olanzapine, a lower D₂RO (i.e., 50%) seems a more reasonable marker of AP efficacy. Interestingly, using 123I-IBZM SPECT Frankle et al. (2004) reported 69 ± 8% and 55 ± 11% D₂RO induced by risperidone 6 mg/day and olanzapine 10 mg/day, respectively, and that at these doses, 48% D₂RO would be necessary to reduce stimulation of D₂ receptors by dopamine to levels similar to those measured in healthy subjects. Our study results suggest that clinical response to these AP may be maintained with 123I-IBZM measured D₂RO values below 65%. However, neither an efficacy threshold model has been empirically confirmed in atypical AP, nor a direct comparison of the D₂RO values measured with PET and SPECT in the same patient has been made. Moreover, it is unclear if the threshold for inducing response is the same as the one for maintaining it, that is in chronically dosed, stabilized patients (Kapur et al., 1999; Nyberg et al., 1995). For clozapine, large interindividual variability in D₂RO has already been reported (Nordström et al., 1995a; Pickar et al., 1996), probably due to the high interindividual variations in plasma unbound fraction for this AP and its high interindividual C_p variability (Darby et al., 1997). Clozapine showed the lowest variance explained by C_p in the PK–D₂RO model (10%). This may be explained by the irregular distribution of experimental data at low C_p values, that is below 350 ng/mL, as shown in Figure 1. Similar distributions can be found in previous SPECT (Pickar et al., 1996) and PET (Kapur et al., 1999) studies. This observation supports the 350 ng/mL value as the lower limit of the optimal C_p range reported for clozapine efficacy in treatment-refractory schizophrenics.
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D_{2RO} versus dose (mg/kg) profiles found in this study match with those reported by Dresel et al. (1999) and Meisenzahl et al. (2000) for risperidone and by Schmitt et al. (2002) for olanzapine. Interestingly, these authors used very similar methodology and the same equipment to the one used in this study. D_{2RO} versus dose (mg/kg) profiles reported by other groups using different equipment (Scherer et al., 1994; Pickar et al., 1996; Knable et al., 1997; Dresel et al., 1998; Lavalaye et al., 1999; Tauscher et al., 1999) are also in agreement, although a trend to lower D_{2RO} values is sometimes seen in this study. To the best of our knowledge, there are no published SPECT studies reporting D_{2RO} versus dose or C_p for quetiapine.

Sigmoidal E_{max} models have been mainly reported using PET. D_{2RO\text{MAX}} results of this SPECT study are in agreement with those reported using PET by Kapur et al. (1999) for risperidone, olanzapine and clozapine, and with the only SPECT report that was found for risperidone in the literature search (Knable et al., 1997). Although D_{2RO\text{MAX}} for olanzapine was 100%, it was lower for risperidone and particularly for clozapine and quetiapine. This may suggest partial saturability of striatal D_2 receptors by these AP or, more likely, be a consequence of the low D_{2RO} induced by the C_p seen in clinical practice. Higher C_p than those seen at clinically relevant doses are expected to induce complete striatal occupancy (Nyberg et al., 2002). EC_{50} values reported in PET studies are usually lower (3.2–10.3 ng/mL) (Kapur et al., 1998, 1999; Remington et al., 1998; Nyberg et al., 1999), than the ones found in the present study for risperidone and olanzapine (22.7–23.1 ng/mL). Methodological differences (e.g., radioligand, image processing and quantification) are more likely to account for

Figure 3  Comparison of the steady state C_p over time (left) and corresponding D_{2RO\text{Sim}} (right), plotted against time after dose intake. Curves represent mean (continuous line) and percentiles 5 and 95 (dashed lines) for a single representative dose for each AP. C_p, R_{HR\text{90}}, C_p, O, C_p, C_p, and C_p are C_p for risperidone active moiety, olanzapine, clozapine and quetiapine, respectively.
this difference than biological factors. The $D_{2}\text{RO}$ versus $C_p$ profiles found in the present study match with values reported by Talvik et al. (2001) for clozapine and by Kapur et al. (2000a), Gefvert et al. (2001) and Tauscher-Wisniewski et al. (2002) for quetiapine, although no PK–$D_{2}\text{RO}$ relationship was reported by these authors.

$D_{2}\text{RO}$ over time was stabilized and dissociated from PK for risperidone, olanzapine and clozapine. Olanzapine showed the maximum stability, followed by risperidone and clozapine. In contrast, quetiapine $D_{2}\text{RO}$ over time was variable and associated with its PK levels over time (Figure 3). These results are in agreement with $^{11}C$-Raclopride PET studies by Tauscher et al. (2002a), Jones et al. (2000) and Kapur et al. (1999) reporting either a slow decline or a sustained occupancy over time for risperidone and olanzapine. For clozapine, $D_{2}\text{RO}_{\text{in}}$ in this SPECT study adequately predicted the $D_{2}\text{RO}$ level reported by Jones et al. (2000) 48h after drug intake (0–18% versus 15%) and times of peak occupancy found by Nordström et al. (1995) (1.6–3.2 versus 3.6h). Similarly, transient high striatal $D_{2}\text{RO}$ within 1–3 h of the administration of quetiapine, declining rapidly after dose intake has been reported using $^{11}C$-Raclopride PET by Jones et al. (2000), Gefvert et al. (2001), Kapur et al. (2000a) and Tauscher-Wisniewski et al. (2002), in agreement with the results of the present SPECT study. In some cases, a trend to lower $D_{2}\text{RO}$ values was predicted by our study in comparison to $D_{2}\text{RO}$ reported by other authors at the same times, which may be explained by underlying differences of the PET and SPECT procedures. Further studies are planned to clarify this issue.

Theoretically, the combination of the rate of AP dissociation from the $D_{2}$ receptor and their plasma $T_{1/2}$ are likely responsible for the maintained or transient-peak $D_{2}\text{RO}$ time course (Kapur and Seeman, 2000; Tort et al., 2006). Based on the relationship between $C_p$ and $D_{2}\text{RO}$ found for the four AP, higher variation in $D_{2}\text{RO}$ is expected in the steeper part of the PK–$D_{2}\text{RO}$ curve. Many of the patients on risperidone and olanzapine in this study were in this ascending part of the curve. Thus, the prolonged $D_{2}\text{RO}$ seen with olanzapine might be better explained by the long plasma $T_{1/2}$ found for this AP. For risperidone, the presence of the long-acting active metabolite 9-hydroxy-risperidone, responsible of the majority of the $C_p$ of the active moiety and with acknowledged longer $T_{1/2}$ than the parent compound, may have contributed to the prolonged $D_{2}\text{RO}$ (Schotte et al., 1996; Seeman, 2005).

The potential influence of the degree of protein binding for each of the four APs studied on the modelled data should be discussed. Risperidone, olanzapine and clozapine are equally highly bound to plasma proteins (90%) while the protein binding of quetiapine is of 83% (Jann, 2002). Based on these data and assuming that only the free fraction of the drug crosses the blood/brain barrier, the estimated relative ratio between the $EC_{50}$ for risperidone, olanzapine and clozapine provides an estimate of the relative potency of these three compounds, assuming a similar blood-to-brain ratio. However, a fair comparison of the quetiapine potency with the potency of the other APs would require a correction of the model estimated $EC_{50}$ by increasing this value about 8%.

Limitations of the study

Several potential limitations of the SPECT procedure applied in this study deserve discussion. First, $D_{2}\text{RO}$ should ideally be calculated as the percentage difference between the available number of $D_{2}$ receptors measured after treatment with respect to those initially available in a drug naïve or free condition in the same subject. However, scanning a patient in these conditions is difficult and too often unfeasible. For this reason, calculation of $D_{2}\text{RO}$ using the mean receptor availability value from a control group (often healthy volunteers) is extensively used in the literature either using SPECT (Knable et al., 1997; Dresel et al., 1999; Tauscher et al., 1999) or PET (Gefvert et al., 1998; Kapur et al., 1999; Talvik et al., 2004). Second, there is evidence using $^{11}C$-raclopride PET of approximately 5% decrease per decade in $D_{2}$ receptor availability above the age of 30 years (Rinne et al., 1993; Antonini et al., 1993).

$^{123}$I-IBZM specific uptake was not corrected by age in this study. However, this should not affect the results since there were no statistical differences in age between the control group and the patient groups. Therefore, the potential bias in the $D_{2}\text{RO}$ values due to lack of age-correction, if any, should be small. Finally, a single bolus injection and ratio method at pseudo-equilibrium was used for quantification. Ideally, a bolus + constant infusion approach or a model-based multiple-scan method would more accurately estimate the binding potential. However, the single bolus and ratio method at pseudo-equilibrium is widely used because the radioactive dose administered is kept to a minimum, subjects are more likely to participate in a single-scan experiment, there are far smaller errors in head repositioning and the whole experiment is conducted in one session, thus avoiding possible diurnal or longer term variations in receptor measures (Laruelle, 2000). Furthermore, the bolus injection approach yields acceptable results and has been extensively used in the SPECT and PET literature (Pilowsky et al., 1996; Dresel et al., 1999; Tauscher et al., 1999; Lavlaye et al., 1999; Nyberg et al., 1999; Talvik et al., 2001).

Conclusions

A wide range of both observed $C_p$ and $^{123}$I-IBZM SPECT measured $D_{2}\text{RO}$ is obtained at therapeutic doses of risperidone, olanzapine, clozapine and quetiapine in clinically stabilized schizophrenic patients. The findings in this study suggest that clinical response to these APs may be maintained with $D_{2}\text{RO}$ values below 65%. The relationship between PK and striatal $D_{2}\text{RO}$ is adequately described by a PK–$D_{2}\text{RO}$ sigmoidal $E_{max}$ model for the four AP. $D_{2}\text{RO}$ patterns over time differ between AP, being stabilized and dissociated from PK for risperidone, olanzapine and clozapine, but variable and PK-associated for quetiapine. These results should be considered for accurate interpretation of $D_{2}\text{RO}$ measurements, proper design of studies and optimization of AP drug regimens.

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Appendix

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