Comparison of D₂ dopamine receptor occupancy after oral administration of quetiapine fumarate immediate-release and extended-release formulations in healthy subjects

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Abstract

Quetiapine is an established drug for treatment of schizophrenia, bipolar disorder, and major depressive disorder. While initially manufactured as an immediate-release (IR) formulation, an extended-release (XR) formulation has recently been introduced. Pharmacokinetic studies show that quetiapine XR provides a lower peak and more stable plasma concentration than the IR formulation. This study investigated if the pharmacokinetic differences translate into different time curves for central D₂ dopamine receptor occupancy. Eleven control subjects were examined with positron emission tomography (PET) and the radioligand [¹¹C]raclopride. Eight subjects underwent all of the scheduled PET measurements. After baseline examination, quetiapine XR was administered once-daily for 8 d titrated to 300 mg/d on days 5–8, followed by 300 mg/d quetiapine IR on days 9–12. PET measurements were repeated after the last doses of quetiapine XR and IR at predicted times of peak and trough plasma concentrations. Striatal D₂ receptor occupancy was calculated using the simplified reference tissue model. Peak D₂ receptor occupancy was significantly higher with quetiapine IR than XR in all subjects ($50 \pm 4\%$ and $32 \pm 11\%$, respectively), consistent with lower peak plasma concentrations for the XR formulation. Trough D₂ receptor occupancy was similarly low for both formulations (IR $7 \pm 7\%$, XR $8 \pm 6\%$). The lower peak receptor occupancy associated with quetiapine XR may explain observed pharmacodynamic differences between the formulations. Assuming that our findings in control subjects are valid for patients with schizophrenia, the study supports the view that quetiapine, like the prototype atypical antipsychotic clozapine, may show antipsychotic effect at lower D₂ receptor occupancy than typical antipsychotics.

Introduction

Quetiapine is an atypical antipsychotic drug with efficacy demonstrated in clinical trials for the treatment of schizophrenia, bipolar disorder, major depressive disorder, and generalized anxiety disorder. The clinical effects are thought to be mediated by both quetiapine and its main active human metabolite, norquetiapine (Jensen *et al.* 2008). Quetiapine in its original immediate-release (IR) formulation has a short half-life (7 h) (Nemeroff *et al.* 2002) and twice-daily administration is recommended for the treatment of schizophrenia and bipolar mania. To allow for once-daily dosing, an extended-release (XR) formulation has more recently been developed. Pharmacokinetic studies have shown that, when given in equivalent daily doses, the exposure in terms of area under the curve (AUC) of the two compounds is comparable. Whereas the XR formulation has a slightly lower peak plasma concentration (C_{max}) than the

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IR formulation, it has a longer half-life (Figueroa *et al.* 2009).

To explore if there may be clinically important pharmacodynamic differences between the two formulations, it is of interest to establish if the difference in pharmacokinetic profile translates into different brain exposure and time-course of central receptor occupancy. Positron emission tomography (PET) studies of D_2 dopamine receptor occupancy have been well validated and demonstrated to have high test–retest reproducibility (Nyberg *et al.* 1996), with D_2 receptor occupancy showing a curvilinear relationship with plasma drug concentrations. In patients treated with quetiapine, PET studies have confirmed occupancy of the D_2 receptor in the human brain. A marked fluctuation in D_2 receptor occupancy during a dosing interval has been shown in patients treated with quetiapine IR at clinically relevant doses. Several studies have reported moderate D_2 receptor occupancy (range 29–74%) at peak plasma levels, whereas D_2 receptor occupancy has been low or undetectable at trough plasma levels (Gefvert *et al.* 1998; Kapur *et al.* 2000*b*; Mamo *et al.* 2008; Tauscher-Wisniewski *et al.* 2002). To date, quetiapine in the new XR formulation has been examined in a single study (Mamo *et al.* 2008). In the cross-over study by Mamo and colleagues 12 patients with schizophrenia or schizoaffective disorder were assigned to one of three dose groups of quetiapine (300, 600 or 800 mg/d). D_2 occupancy was compared at estimated times of peak and trough plasma concentrations (T_{max} and T_{min}, respectively) of equivalent daily doses of quetiapine XR and IR. There was no statistically significant difference in D_2 receptor occupancy between the formulations. However, the study cannot be viewed as conclusive, since the lack of a reported difference could be due to a large spread in plasma concentrations and the small sample size in each dose group ($n=4$). Moreover, the PET measurements at expected IR peak were performed 1 h post-administration and the T_{max} of the IR formulation has been reported to be 2 h (Figueroa *et al.* 2009). Consequently, the D_2 occupancy at IR peak in this study might have been underestimated, as plasma concentrations were not measured throughout the dosing interval to confirm that PET measurements were performed at true peak concentration.

The primary aim of the present study was to compare striatal D_2 receptor occupancy with quetiapine IR and XR in equal doses. A secondary purpose was to examine the temporal relationship between the plasma concentration of quetiapine and D_2 receptor occupancy. Eleven control subjects were examined with PET and the radioligand [^{11}C]raclopride, before and after treatment with 300 mg/d quetiapine XR and IR, respectively. The D_2 receptor occupancy values of the present study are discussed in relation to literature values for classical (typical) and atypical antipsychotic drugs.

Method

Study design

The study was conducted as a research collaboration between AstraZeneca, Södertälje, Sweden and the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, and was approved by the local Ethics and Radiation Safety Committees and the Medical Products Agency in Sweden. The study was designed as an open label, one-sequence cross-over study, where each subject was his own control.

Study subjects

Eleven males aged between 21 and 29 yr (25 ± 2.5, mean$\pm$s.d.) were recruited from an AstraZeneca database of subjects who expressed an interest in participating in clinical studies. The subjects were healthy according to medical history including psychiatric symptoms and physical examination including ECG, routine blood tests, and magnetic resonance imaging (MRI) examination of the brain. A negative urine drug screen was required for inclusion. No prescribed drugs were allowed from 7 d before the first PET measurement and throughout the study. The use of nicotine products was forbidden and caffeine intake was restricted to a maximum of five cups per day. The intake of these substances was monitored at an AstraZeneca study unit, where subjects were supervised throughout the study period. All subjects gave verbal and written consent after receiving a description of the study.

Administration of study drug and PET measurement schedule

Quetiapine was administered orally, once-daily, in the morning for 12 d. After 4 d of dose titration of quetiapine XR from 50 mg up to 300 mg, each subject received 300 mg/d quetiapine XR for 4 d. Treatment was then directly switched to 300 mg/d quetiapine IR for 4 d.

Each subject participated in five PET measurements in total. The measurements were performed at drug-free conditions (baseline), at expected maximum plasma concentration (C_{max}) of quetiapine – which has been reported to be at 2 h after the quetiapine IR dose

and 5 h after the XR dose (Figueroa *et al.* 2009) – and at trough plasma concentration (C_{min}). The PET measurements at C_{max} were performed on the fourth day of administration of XR and IR, respectively, whereas the measurements at C_{min} were performed on the morning after the last dose of each formulation.

Determination of plasma concentrations

Blood samples for determination of plasma concentrations of quetiapine and norquetiapine were collected on the last day of treatment with the respective formulations. For quetiapine XR, samples were drawn pre-dose and at 0.5, 1, 2, 3, 4, 5, 5.5, 6, 8, 12, 24 and 25 h post-dose. For quetiapine IR, samples were obtained pre-dose and at 0.5, 1, 1.5, 2, 2.5, 5, 11, 24 and 25 h post-dose. The differences in sampling times for the two formulations were to allow for dense sampling at expected T_{max}. The samples were analysed by BASi (Bioanalytical Systems Inc., USA) by a liquid chromatography–tandem mass spectrometry (LC–MS/MS) method described in detail elsewhere (Davis *et al.* 2010). The lower limit of quantification is <0.70 ng/ml (corresponding to <1.8 nmol/l quetiapine) (Davis *et al.* 2010).

MRI and PET measurements

MRI T_1-weighted images were acquired using a 1.5 T GE Signa system (GE Medical Systems, USA). PET examinations were performed using high-resolution research tomography (HRRT; Siemens Molecular Imaging, USA) with a spatial resolution of $\sim$1.5 mm full-width-half-maximum (FWHM) (Varrone *et al.* 2009). A plastic helmet made individually for each subject was used during each PET examination in order to minimize head movements and to ensure maintenance of the same head position in all experiments.

[^{11}C]raclopride was prepared by methylation of the corresponding desmethyl precursor using [^{11}C]methyl triflate, as described previously (Langer *et al.* 1999). At each examination, a saline solution containing [^{11}C]raclopride with a radioactivity of 201–236 MBq was injected in the antecubital vein as a bolus over 2 s. The specific radioactivity at the time of injection exceeded 1900 Ci/mmol and the injected ligand mass was on all occasions <5 μg. This low mass does not cause any substantial mass effect of the ligand (Farde *et al.* 1995). Radioactivity in the brain was measured continuously over 63 min. The radioactivity from each PET measurement was reconstructed in a series of time-frames consisting of four 15-s, four 30-s, six 1-min, six 3-min and six 6-min frames.

Regions of interest (ROIs)

The MR images were realigned to the anterior–posterior commissure plane. ROIs were manually delineated on the realigned MR images for each subject using software originally developed for the Human Brain Atlas (Roland *et al.* 1994). Left and right putamina were drawn on 6–8 (number depending on individual anatomy) sagittal sections of the brain in concordance with the anatomical limits. The cerebellum was depicted on six adjacent central horizontal sections. MR images were co-registered to averaged PET images using statistical parametric mapping software (SPM5, Wellcome Department of Cognitive Neuroscience, UK). ROIs were then transferred to the series of PET images to generate time–activity curves.

Calculation of binding potential (BP) and D₂ receptor occupancy

The BP in each PET measurement was calculated using the simplified reference tissue model, with the putamen as ROI and the cerebellum as reference region (Lammertsma & Hume, 1996). BP refers in this context to BP_{ND}, which represents the ratio at equilibrium between the concentration of specifically bound radioligand and that of the non-displaceable radioligand in tissue (Innis *et al.* 2007).

The D₂ receptor occupancy at peak and trough concentration was calculated for each subject according to the equation:

$$Occ = \frac{BP_{baseline} - BP_{drug}}{BP_{baseline}} \times 100, \tag{1}$$

where Occ is the D₂ receptor occupancy, $BP_{baseline}$ is the BP in the drug-free state, and BP_{drug} is the BP measured at the respective time-points (peak and trough) of drug treatment.

Calculation of apparent inhibition constant ($K_{i,app}$)

When assuming a linear relationship between drug concentration in brain and drug concentration in plasma, the relationship between D₂ receptor occupancy and plasma drug concentration can be described by a curvilinear function according to the expression:

$$Occ = \frac{Occ_{max} \cdot C_p}{K_{i,app} + C_p}, \tag{2}$$

where Occ_{max} is the maximal D₂ receptor occupancy induced by the drug and C_p is the plasma concentration of the drug (Karlsson *et al.* 1995). $K_{i,app}$ is an affinity constant corresponding to the drug plasma

concentration required to occupy 50% of available receptors. D_2 receptor occupancy values were plotted *vs.* the corresponding plasma concentrations of quetiapine at the PET measurements. From the measured values of occupancy and concentration, $K_{i,app}$ was determined by fitting equation (2) to experimental data using a nonlinear least-squares minimization procedure. Occ_{max} was fixed to 100%, as it has been previously demonstrated that 100% D_2 receptor occupancy is approached for [^{11}C]raclopride binding during treatment with high doses of antipsychotic drugs (Nyberg *et al.* 1998).

The 'active moiety'

To allow comparisons with previous studies of D_2 receptor occupancy after quetiapine treatment, the initial calculation of $K_{i,app}$ and the estimated time curve for D_2 receptor occupancy were based on the plasma concentration values for quetiapine only. The affinity of the main metabolite, norquetiapine, for the D_2 receptor *in vitro* is of the same order as that for quetiapine (Jensen *et al.* 2008). Assuming similar affinity and similar passage across the blood–brain barrier in human subjects *in vivo*, the plasma concentration values of quetiapine and norquetiapine were summed to obtain a value for the 'active moiety'. This approach has previously been applied for risperidone and its active metabolite, 9-OH risperidone (Cohen, 1994; Nyberg *et al.* 1993, 1999). In the calculation of $K_{i,app}$, the explanatory power of the active moiety was compared to quetiapine alone.

Estimation of the time curve for D_2 receptor occupancy during a dosing interval

To obtain a time curve for D_2 receptor occupancy throughout a dosing interval, the calculated $K_{i,app}$ was entered in equation (2) together with the mean plasma concentration of quetiapine at each time-point. To enable comparisons between the two formulations, results were plotted separately for quetiapine XR and IR.

Statistics

A two-tailed, two-sample *t* test was used to compare the mean plasma concentrations achieved at peak and trough. The same test was used to compare mean D_2 receptor occupancy with quetiapine IR and XR at C_{max} and C_{min}. Neuroreceptor occupancy is not normally distributed, due to the curvilinear relationship between plasma concentration and occupancy, and occupancy values can thus not be expected to be

normally distributed. However, at low concentrations, the curve is approximately linear, which may allow the use of a parametric test. In the present study, the maximal mean D_2 receptor occupancy measured at peak was 59% and therefore the *t* test was also applied to test differences at peak occupancies.

To ensure that quetiapine plasma concentration at T_{max} was not significantly different from quetiapine plasma concentration during peak PET measurements, the *t* test was also applied to compare mean C_{max} with mean concentration during peak PET ($C_{av,PET,peak}$) for the respective formulations.

The statistical analysis was performed using SAS statistical software JMP 8 (SAS Institute, USA).

Results

Of the 11 subjects enrolled in the study, eight underwent all of the scheduled PET examinations according to protocol. One subject discontinued before the fourth PET measurement due to an adverse event (panic attack, anxiety), and PET measurements and plasma concentrations during treatment with the IR formulation were therefore not obtained from this subject. Due to synthesis failure of the radioligand, PET at XR trough was not performed for one subject and PET at IR peak was delayed 3.5 h for another subject. D_2 receptor occupancy and plasma concentration values from the delayed PET measurement were not included in the analysis, as the timing of this measurement did not correspond to the time of peak concentration.

Plasma concentrations

The plasma concentrations of quetiapine were maximal at about 1.7 h after treatment with the IR formulation and about 5 h after administration of the XR formulation (Table 1, Fig. 1). C_{max} for quetiapine (mean $\pm$ S.D.) was 1850 ± 820 nmol/l and 894 ± 380 nmol/l for the IR and XR formulations, respectively. The difference between formulations was statistically significant (d.f. = 11.0, $t = 3.18$, $p < 0.01$). At T_{max}, the concentration of norquetiapine was 624 ± 100 nmol/l for IR and 346 ± 110 nmol/l for XR (d.f. = 17.0, $t = 5.55$, $p < 0.0001$).

For both formulations, the mean trough concentrations of quetiapine during PET were significantly lower than the mean peak concentrations (IR: d.f. = 8.0, $t = 6.66$, $p = 0.0002$; XR: d.f. = 9.2, $t = 6.82$, $p < 0.0001$) (Fig. 1). Concentrations of quetiapine were 20.3 ± 7.8 nmol/l for IR and 69.9 ± 40 nmol/l for XR during the second (trough) PET measurement. The difference was statistically significant (d.f. = 9.7,

Table 1. Summary statistics of pharmacokinetic parameters of quetiapine and norquetiapine (PK analysis set)

Analyte	Treatment	N	T_{max} (h) Mean (s.d.)	C_{max} (nmol/l) Mean (s.d.)	AUC, 0–24 (h per nmol/l) Mean (s.d.)	$C_{av,PET,peak}$ (nmol/l) Mean (s.d.)	$C_{av,PET,trough}$ (nmol/l) Mean (s.d.)
Quetiapine	XR	10	5 (2.6)	894 (380)	8770 (3700)	719 (310)	69.9 (40)
	IR	9	1.7 (0.7)	1850 (820)	8130 (2700)	1460 (510)	20.3 (7.8)
Norquetiapine	XR	10	6 (3.3)	346 (110)	5740 (2100)	290 (120)	141 (57)
	IR	9	2.1 (0.5)	624 (100)	6100 (1400)	554 (91)	111 (42)

T_{max}, Time of peak plasma concentration; C_{max}, peak plasma concentration; AUC, area under the curve; $C_{av,PET,peak}$, average concentration of drug in plasma during PET examination at expected peak; $C_{av,PET,trough}$, average concentration of drug in plasma during PET examination at expected trough.
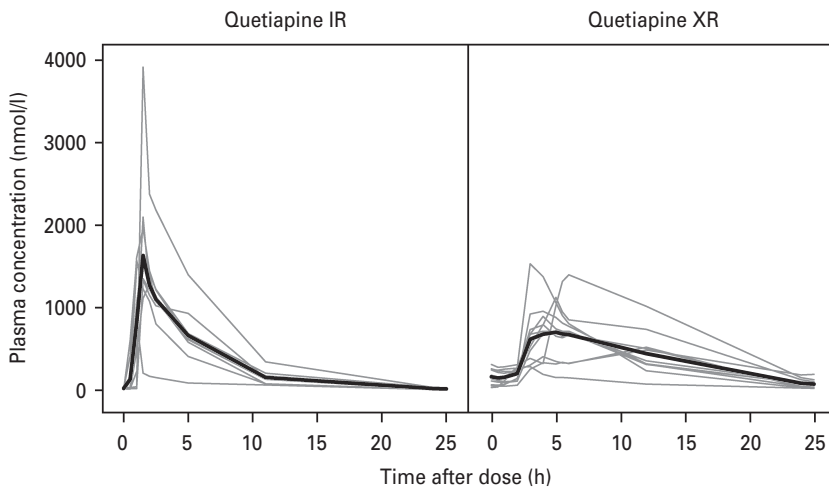

Fig. 1. Arithmetic mean plasma concentration of quetiapine and norquetiapine during quetiapine IR (left) and XR (right) administration.

$t = 3.82$, $p < 0.005$). Trough concentrations of norquetiapine were 111 ± 42 and 141 ± 57 nmol/l for IR and XR, respectively. This difference was not statistically significant (d.f. $= 16.4$, $t = 1.32$, $p = 0.2$).

D_2 receptor occupancy

The PET measurements were performed close to the observed peak concentrations of quetiapine and norquetiapine, respectively. The time difference between the start time of the PET peak measurements and T_{max} of quetiapine were: IR (0.14 ± 0.43 h, range -0.55 to 0.9) and XR (0.12 ± 2.6 h, range -6.76 to 2.24). Thus, a larger range was noted for the XR formulation, but the more blunted plasma concentration curve with this formulation makes the timing of the PET measurement less sensitive to deviations from T_{max}. The difference between quetiapine C_{max} and the plasma concentration measured during the peak PET

measurements ($C_{av,PET,peak}$) was not statistically significant for either formulation (IR: C_{max} 1850 ± 820 *vs.* $C_{av,PET,peak}$ 1460 ± 510, d.f. $= 13.3$, $t = 1.20$, $p = 0.25$; XR: C_{max} 894 ± 380 *vs.* $C_{av,PET,peak}$ 719 ± 310, d.f. $= 17.2$, $t = 1.13$, $p = 0.27$). In all subjects, D_2 receptor occupancy was higher at IR peak compared to XR peak (Figs 2 and 3). The mean D_2 receptor occupancy in the putamen at peak concentration was $50 \pm 4\%$ for quetiapine IR ($n = 9$) and $32 \pm 11\%$ for XR ($n = 11$). The difference was statistically significant (d.f. $= 13.5$, $t = 4.89$, $p = 0.0003$). There was no significant difference in D_2 receptor occupancy at trough levels between the two formulations [IR $7 \pm 7\%$ ($n = 10$), XR $8 \pm 6\%$ ($n = 10$); d.f. $= 17.6$, $t = 0.41$, $p = 0.7$]. In two subjects, trough occupancy even reached negative values (-1% at XR trough for one subject and -3% at IR trough for another subject). However, this minor negativity was within the range for test–retest reliability.
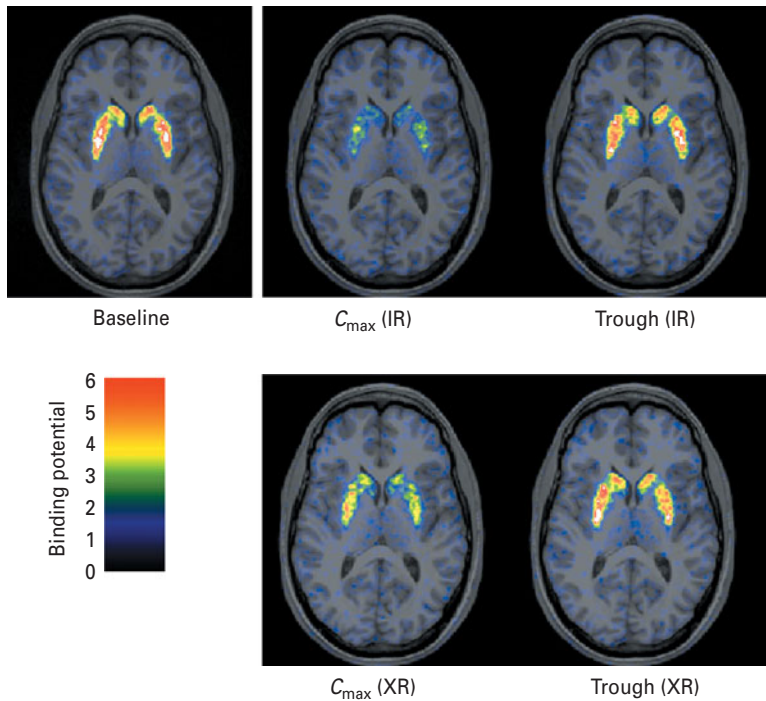
Fig. 2. Parametric horizontal PET images through the caudate putamen level showing the binding potential after intravenous injection of [^{11}C]raclopride in a human subject at baseline conditions and after administration of quetiapine IR and XR, respectively.
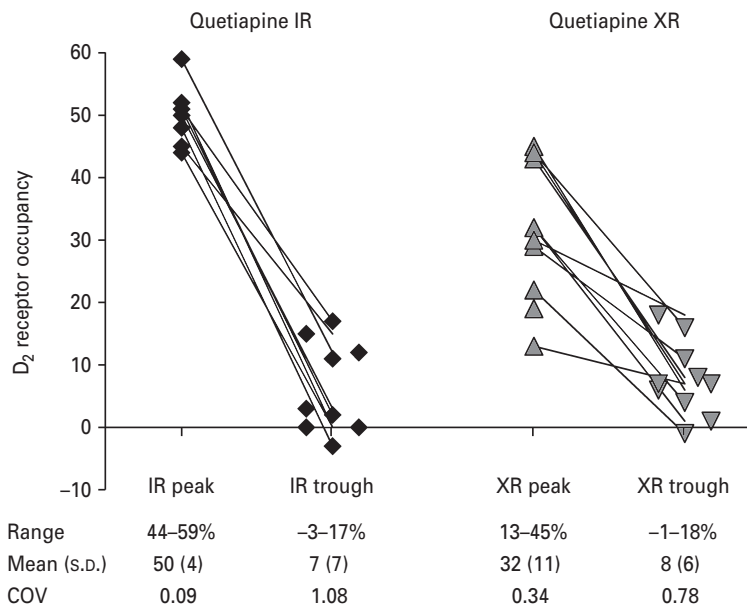

Fig. 3. D$_2$ dopamine receptor occupancy (%) in 11 subjects after administration of quetiapine IR and XR, respectively.

Apparent inhibition constant ($K_{i,app}$)

When using all PET measurements and the concentration of quetiapine measured after administration of IR and XR together, $K_{i,app}$ was calculated to be 1369 nmol/l (Fig. 4). $K_{i,app}$ calculated for quetiapine IR only was 1373 nmol/l and for XR only was 1365 nmol/l. Assuming that quetiapine and
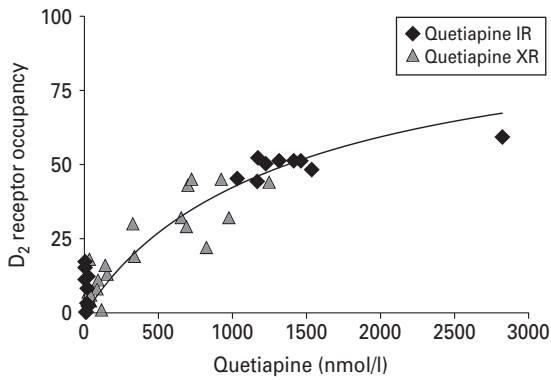
Fig. 4. D_2 dopamine receptor occupancy (%) *vs.* quetiapine plasma concentration (IR and XR formulations).

norquetiapine have the same affinity for the D_2 receptor, the sum of the two concentrations was used as an estimate of the active moiety. $K_{i,app}$ calculated for the active moiety using measurements for both formulations was 2004 nmol/l, and $K_{i,app}$ calculated for IR and XR separately was 1968 nmol/l and 2041 nmol/l, respectively. The explanatory value of quetiapine and norquetiapine alone or in combination (interaction model) was also tested using nonlinear mixed-effects modelling. Goodness of fit was not improved using the interaction model (results not shown).

The mean peak D_2 receptor occupancy measured after treatment with 300 mg of the XR formulation was 32% (range 13–45%). As the relationship between dose and plasma concentration of quetiapine is linear (DeVane & Nemeroff, 2001), it is possible to use equation (2) (see Methods section) to predict the dose required to occupy 50% of the receptor. The calculated $K_{i,app}$ value corresponded to a dose of 638 mg at steady state following once-daily dosing. For the IR formulation, the mean peak D_2 receptor occupancy measured was 50%, thus corresponding to the administered dose of 300 mg at steady state following once-daily dosing.

Estimated D_2 receptor occupancy over time

The time curve for estimated D_2 receptor occupancy during a dosing interval was calculated for both formulations using equation (2) (Fig. 5). After administration of quetiapine IR, a high and transient peak D_2 receptor occupancy was reached within 2 h, after which D_2 receptor occupancy slowly declined. For the XR formulation, peak D_2 receptor occupancy was less pronounced and remained at a higher level compared to IR.

Discussion

In the present PET study, we compared the D_2 dopamine receptor occupancy obtained after administration of 300 mg quetiapine XR and IR once-daily at steady-state conditions. Peak D_2 receptor occupancy was significantly higher ($p=0.0003$) with the IR formulation (Fig. 3), whereas there was no significant difference in trough D_2 receptor occupancy between quetiapine IR ($7\pm7\%$) and XR ($8\pm6\%$). The study confirms that the previously reported pharmacokinetic differences between the two formulations (Figueroa *et al.* 2009) translate into different time curves for D_2 receptor occupancy in the human brain.

The 300 mg daily dose used in the present study is at the lower end of the dose interval recommended for the treatment of schizophrenia, i.e. 150–750 mg for IR and 400–800 mg for XR (Seroquel® Prescribing Information, 2010*a*; Seroquel® XR Prescribing Information, 2010*b*). As for other CNS drugs, previous pharmacokinetic studies of quetiapine IR have shown inter-individual variability in the relationship between dose and plasma concentration (DeVane & Nemeroff, 2001; Hasselstrom & Linnet, 2004).

In clinical practice, quetiapine IR is predominantly administered twice-daily for the treatment of schizophrenia and bipolar mania according to approved labels. However, once-daily dosing of quetiapine IR has shown efficacy in bipolar depression (Calabrese *et al.* 2005). As the primary aim of this study was to achieve a direct comparison of the XR and IR formulations, IR was administered only once-daily. The plasma concentration and corresponding D_2 receptor occupancy can therefore not be directly translated to the more commonly used twice-daily dosing. The peak D_2 receptor occupancy associated with standard 150 mg twice-daily treatment with the IR formulation would, in all probability, be lower than the receptor occupancy obtained in the present study.

The dose of quetiapine XR required to occupy 50% of the D_2 receptor was estimated to be 638 mg (continuous once-daily dosing). The recommended dose of quetiapine XR for the treatment of schizophrenia (i.e. 400–800 mg) would, according to the same equation, correspond to 39–56% occupancy of the D_2 receptor. This estimation is in agreement with the literature, since the average peak D_2 receptor occupancy measured after dosing with 800 mg quetiapine XR has been reported to be 56% (Mamo *et al.* 2008).

For typical antipsychotic drugs, it has been suggested that D_2 receptor occupancy of at least 65–70% is required for an antipsychotic effect, and that the risk of extrapyramidal side-effects (EPS) is high when
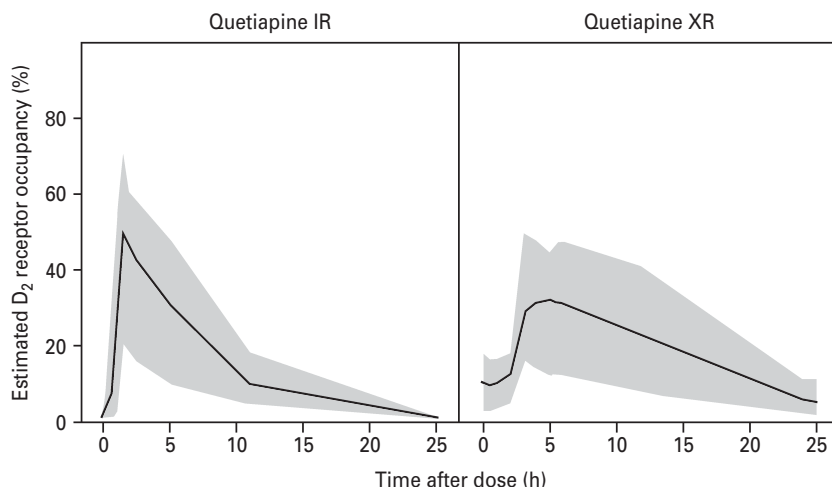
Fig. 5. Estimated D$_2$ dopamine receptor occupancy (%) *vs.* time for quetiapine IR (left) and XR (right) formulations. The solid lines describe the occupancy time curve for a typical individual. The grey areas represent the 95% prediction intervals.

D$_2$ receptor occupancy exceeds 80% (Farde *et al.* 1992; Kapur *et al.* 2000*a*). A therapeutic window of 65–80% D$_2$ receptor occupancy has therefore been suggested. In PET studies with recommended doses of the second-generation antipsychotic drugs, risperidone and olanzapine, D$_2$ receptor occupancy has been within this window (Kapur *et al.* 1999; Nordström *et al.* 1998; Nyberg *et al.* 1999; Tauscher *et al.* 2002). However, the atypical antipsychotic drug, clozapine, has an antipsychotic effect at lower D$_2$ receptor occupancy (20–67%), despite an unsurpassed efficacy in the treatment of schizophrenia (Kane, 1989; Nordström *et al.* 1995). Previous PET studies have shown that quetiapine induces low to moderate D$_2$ receptor occupancy (29–74% at peak, 0–27% at trough) when given at clinical doses (Gefvert *et al.* 1998; Kapur *et al.* 2000*b*; Mamo *et al.* 2008; Tauscher-Wisniewski *et al.* 2002). The results in the present study corroborate these previous observations. Based on calculations using equation (2) (see Methods section), 1185 mg quetiapine XR would be required to achieve 65% D$_2$ occupancy at peak. It can thus not be excluded that quetiapine, like clozapine, induces an antipsychotic effect at low striatal D$_2$ receptor occupancy (for review see Nord & Farde, 2010). However, whether the antipsychotic effect is related to D$_2$ occupancy alone, or if additional mechanisms are involved remains to be elucidated.

The $K_{i,app}$ value can also be used to calculate the quetiapine dose required to exceed 80% of D$_2$ receptor occupancy, above which the risk of EPS is increased (Farde *et al.* 1992; Kapur *et al.* 2000*a*). Interestingly, quetiapine XR doses exceeding 2550 mg ($4 \times K_{i,app}$) would be needed to reach this level. Thus, during

treatment with clinically recommended doses, it is unlikely that D$_2$ receptor occupancy reaches the 80% threshold suggested for EPS. This is in agreement with clinical studies showing a low incidence of EPS in quetiapine-treated patients (Baldwin & Scott, 2009; Weiden, 2007).

A strength of this study is that individual baseline values of BP were used to calculate D$_2$ receptor occupancy. Using this methodology, errors based on individual variability in receptor densities are minimized. However, a critical experimental condition is that D$_2$ receptor occupancy is indeed measured at C_{max}. As the peak is sharp, peak PET measurements with IR are particularly sensitive to errors if T_{max} and the start of PET measurement are not exactly matched. A comparison of the plasma concentration curve with the time of the peak PET measurement for individual subjects shows that the PET measurements in most cases started at T_{max}. In one subject the PET measurement started just after T_{max} and in another subject PET measurement started just before T_{max}, but the peak concentrations were reached within the time-frame of the PET measurements. Peak D$_2$ receptor occupancy values in these two subjects were 45% and 52%, and were thus within the range of other assessments. However, the possibility that D$_2$ receptor occupancy might have been underestimated in these two subjects cannot be excluded. Regarding the XR formulation, peak PET measurements are less sensitive as the time curve for plasma concentration is more blunted.

Pharmacokinetic studies have demonstrated dose equivalence of the two formulations based on the calculated AUC for standardized dosing intervals (Figueroa *et al.* 2009). The present pharmacokinetic

findings confirm similar AUC and consistent K_i values between the formulations (Table 1). However, our study also demonstrates more pronounced fluctuations in D_2 receptor occupancy with quetiapine IR than XR. It cannot be excluded that this difference may result in different pharmacodynamics. Indeed, a recent experimental study comparing quetiapine XR and IR, titrated from 50 mg up to 300 mg once-daily, in 63 healthy subjects demonstrated that quetiapine XR produced significantly less sedation than quetiapine IR during the initial treatment phase (Datto *et al.* 2009).

The findings in this study might seem discrepant to the findings in a previous study of Mamo *et al.* (2008), where no statistical difference in D_2 occupancy was shown between quetiapine IR and XR. An important difference between the studies is that quetiapine IR was given twice-daily in the study of Mamo *et al.* whereas we used a once-daily administration. As already described, the peak occupancy after a twice-daily administration of quetiapine IR would in all likelihood be lower than the peak occupancy after the same dose administered once-daily. The K_i value received from our data was similar for both formulations, indicating that the difference in occupancy between the formulations depends on differences in plasma concentration. As the treatment regimen in the study by Mamo *et al.* did not provide any statistically different peak plasma concentrations of quetiapine IR and XR, this condition could explain the lack of difference in the peak occupancy measured.

Conclusion

Central D_2 dopamine receptor occupancy differentiates quetiapine IR and XR. The more sustained D_2 receptor occupancy after administration of quetiapine XR *vs.* IR makes this formulation appropriate for the once-daily treatment regimen. The findings in the present study support the view that quetiapine may have an antipsychotic effect at moderate and intermediate striatal D_2 receptor occupancy. Further studies are needed to evaluate if the antipsychotic effect of quetiapine depends on D_2 receptor occupancy alone or if, intriguingly, there are additional antipsychotic mechanisms related to other receptor systems.

Acknowledgements

Statement of Interest

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