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ORIGINAL INVESTIGATION

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The time course of binding to striatal dopamine D_2 receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by positron emission tomography

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Abstract Positron emission tomography (PET) and ^{11}C-raclopride were used to assess the time course of binding to central dopamine D_2 receptors by the novel neuroleptic ziprasidone. In a third party blind study, six healthy male control subjects received a predose of 40 mg ziprasidone and were scanned at an interval of between 4 and 36 h post-dose. One additional subject was assigned to placebo predose and was scanned at 4 h post-dose. Binding potential (BP) was compared with that seen in the subject predosed with placebo and with that seen in nine unmedicated normal volunteers. Subjects studied up to 12 h post-dose had BPs that were greater than 2 SD less than the mean BP, indicative of extensive D_2 receptor binding by ziprasidone. With increasing time between dosing and PET scanning there was a curvilinear increase in BP, so that all studies performed at or after 18 h post-dose gave BPs in the normal range (mean±2 SD). Elevated prolactin levels returned to within the normal range by 18 h post-dose. PET measures of binding potential correlated significantly with serum levels of ziprasidone at the time of scanning and less significantly with absolute prolactin levels at the same time.

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Introduction

In those patients who respond to traditional neuroleptics there is considerable evidence that the antipsychotic effect is mediated by the blockade of central dopamine D_2 receptors. Most compelling is the linear correlation between the affinity of drugs for D_2 receptors in animals and antipsychotic potency in man, a relationship that does not hold for any other neuroreceptor (Creese et al. 1976; Seeman et al. 1976; Peroutka and Snyder 1980). Positron emission tomography (PET) and specific ligands for the D_2 receptor have been used to study the D_2 binding properties of neuroleptic drugs in the living human brain. Independent studies have shown that clinically effective (antipsychotic) doses of a variety of classical neuroleptics result in at least 65% occupancy of central dopamine D_2 receptors (Cambon et al. 1987; Farde et al. 1992), with high occupancy demonstrable 2 h after acute administration of neuroleptic (Farde et al. 1986), and a curvilinear relationship between neuroleptic dosage and D_2 occupancy (Cambon et al. 1987; Farde et al. 1988b).

One of the main drawbacks of D_2 receptor antagonists in clinical practice is their propensity for causing extra pyramidal side effects (EPSE). In elegant studies (Farde et al. 1992) have demonstrated that EPSE are much more common with higher D_2 occupancy, with an apparent threshold for EPSE at between 74% and 82% D_2 occupancy, considerably higher than the 65% threshold required for an antipsychotic effect. The threshold hypothesis is an important consideration in determining optimal doses in the preclinical and clinical evaluation of new neuroleptics. We have previously described a dose finding study using PET and ^{11}C-raclopride in the preclinical evaluation in normal volunteers of the novel neuroleptic ziprasidone, a benzisothiazoyl piperazine that has high affinity for both $5HT_2$ (K_i=0.42 nM) and D_2 (K_i=4.8 nM)

Table 1 Details of the seven subjects studied: time of PET scan post-dose, serum levels of ziprasidone and prolactin at the time of PET scanning, prolactin response and striatal binding potential

Subject	Age (years)	Weight (kg)	Ziprasidone dose (mg)[a]	Time of PET (h post-dose)	Ziprasidone		Prolactin		Binding potential (±SE[c])
					At time of PET (ng/ml)	AUC[0–36][b] ng·h/ml	Peak-baseline mIU/l	At time of PET mIU/l	
1	26	83	Placebo	4	0	0	–67	145	2.67 (±0.04)
2	20	112	40	12	15.3	469	526	206	1.26 (±0.08)
3	23	73	40	27[d]	2.2	426	1143	85	2.46 (±0.05)
4	23	64	40	4	87.9	806	2072	848	0.55 (±0.02)
5	28	84	40	8	33.3	421	625	434	0.85 (±0.02)
6	33	82	40	18	9.8	979	1455	252	1.81 (±0.17)
7	32	84	40	36	0.5	376	682	N/A	2.28 (±0.05)
(8)[e]	34	66	40	6	44.6	511	767	432	0.51 (±0.03)

[a] Investigators performing the PET scans and analysis were blind to treatment allocation
[b] AUC [0–36]: area under the serum concentration-time curve from time 0–36 h
[c] Standard errors of estimate were calculated from the differences between predicted and measured data, as described by Carson (1986)
[d] For technical reasons the PET scan scheduled for 24 h post-dose was postponed to 27 h post-dose. Blood samples taken at 24 h
[e] Additional subject from previous dose-finding study (Bench et al. 1993) who received 40 mg ziprasidone, 5.75 h post-dose

receptors (Seymour et al. 1993; Zorn et al. 1993). This study showed that a dose of between 20 and 40 mg of Ziprasidone caused a level of D_2 occupancy that would be predicted to have antipsychotic efficacy, with 40 mg producing an decrease in binding potential of 77% in comparison with a group of normal controls (Bench et al. 1993).

In addition to the studies which have examined the relationship between antipsychotic efficacy, neuroleptic dose and D_2 occupancy, a smaller number of studies have examined the time course of receptor occupancy after withdrawal of neuroleptics. Thus Cambon et al. (1987) showed that in eight patients withdrawn from neuroleptics, D_2 occupancy returned to normal levels (nil) within a few days, and in one patient within 24 h, whereas Farde et al. (1988b) did not detect a significant decrease in receptor occupancy for up to 54 h. Baron et al. (1989) found that return to normal receptor availability as measured with PET occurred within 5–15 days. In a series of 21 PET studies in ten subjects, Smith et al. (1988) reported a significant increase in available D_2 sites 24 h after withdrawal of haloperidol and by 156 h receptor availability was within the control range.

In this study we used PET and ^{11}C-raclopride to measure binding potential in normal volunteers after a single oral dose of 40 mg ziprasidone. By examining the subjects at different time points after dosing, we hoped to infer the time course of binding to D_2 receptors. While standard pharmacokinetic and prolactin studies in normal volunteers support a twice daily dosage regimen with this drug for therapeutic trials, the present study aimed to determine whether a once or twice daily dosage regimen is appropriate for such trials based on washout of ziprasidone from central D_2 receptors. Blood samples were also taken to allow cross correlations between prolactin levels, plasma concentrations of ziprasidone and binding potential as assessed by PET.

Materials and methods

Subjects

Seven healthy male volunteers between the ages of 20 and 33 were studied. Health was assessed by medical history, full clinical examination, haematological and biochemical profile and urinalysis. All subjects were neuroleptic naive and were not taking any medications at the time of the study. Demographic details of the subjects are shown in Table 1. All subjects gave informed written consent and local ethics committee approval was obtained. Permission to administer radioisotopes was obtained from the Administration of Radioactive Substances Advisory Committee of the UK.

Synthesis of ^{11}C-raclopride

^{11}C-raclopride was prepared at the Cyclotron Unit according to the method of Farde et al. (1988a). The mean specific activity of the seven preparations was 22708 MBQ/mmol (range 10624–31937). Raclopride tartrate was provided by Astra Research Centre, Sweden.

Drug administration and positron emission tomography

Using a third party blind design, the seven subjects were allocated to receive either 40 mg ziprasidone (six subjects) or placebo (one subject). All investigators knew there was only a single subject to be predosed with placebo. Those responsible for the PET procedure and analysis (C.J.B., A.A.L., P.M.G.) were blind to allocation until the data were fully analysed. In practice, two subjects were clearly sedated at the time of PET scanning, thus identifying them as being allocated to active treatment. Subjects were dosed in the fasting state at times that varied between 0400 and 1800 h and PET scans were performed between 1000 and 1630 h, corresponding to times varying between 4 and 36 h post-dose. For technical reasons the PET scan scheduled for 24 h post-dose could not be performed until 27 h post-dose. The placebo pre-dosed subject was randomly inserted into the schedule. PET scans were performed on a CTI 931-08/12 (CTI, Knoxville, Tennessee, USA) scanner (Spinks et al. 1988), which has an axial full width half maximum (FWHM) resolution of 7 mm and an in-plane FWHM resolution of 8.5×8.5 mm. Subjects were aligned in the scanner using a laser system so that the detectors were parallel to the orbito-

meatal line. A pillow containing polystyrene chips and air was used in each case. Evacuation of air from the pillow ensured the subject's comfort and relative immobility. A 10-min transmission scan for correction of tissue attenuation of 511 keV gamma radiation was collected using a retractable $^{68}Ga/^{68}Ge$ ring source.

All seven subjects received bolus intravenous injections of saline solutions (pH 6.0) of ^{11}C-raclopride (mean=10.2 mCi, SD=0.13; mean weight of cold raclopride injected was 6.8 µg, SD=3.0). Dynamic PET scans were collected from the time of injection for a period of 60 min, divided into 25 time frames. Frame length was increased from 5 s initially to 10 min at the end of the study. Venous blood samples for estimation of serum concentrations of ziprasidone were taken predose and at 1, 2, 4, 6, 8, 12, 24 and 36 h post-dose. Additional samples for prolactin assay were taken at the same time points up to 24 h post-dose.

Ziprasidone pharmacokinetic analysis

The details of this analysis have been described previously (Bench et al. 1993). The assay has a dynamic range of 0.5–50 ng/ml, with a lower limit of quantitation of 0.5 ng/ml (Pfizer Central Research, Groton, Conn., USA). The area under the serum ziprasidone concentration-time curve from time 0 to 36 h (AUC[0–36]) was estimated using the trapezoid method.

Prolactin assay

Plasma prolactin (PRL) levels were determined by radioimmunoassay with intra- and interassay coefficients of variation of 2.5% and 6.7%, respectively, and a lower limit of detection of 34 mIU/l, normal range 80–300 mIU/l (Maurer et al. 1986). The PRL response was analysed as the peak-baseline value. The baseline PRL level was determined from a sample taken 1 h before pre-dosing.

Image analysis and modelling of data

The dynamic PET scans were analysed using image analysis software (Analyze version 5.0, Biodynamics Research Unit, Mayo Foundation, USA) on Sun SPARC Workstations. Standard templates for the striatal and cerebellar regions of interest were defined on the raclopride scans, summated to include activity between 30 and 60 min post-injection. The position of the regions were determined by inspection. Regions of interest were defined for caudate (one circular region each side, 4 pixels in diameter; 1 pixel=2.05×2.05 mm), putamen (three contiguous circular regions each side, 4 pixels diameter each) and cerebellum (one circular region each side, 16 pixels diameter). All regions of interest were defined on two adjacent planes using regions of identical sizes. Average values for each anatomical structure were calculated (Sawle et al. 1990; Bench et al. 1993).

The definition of the striatal regions of interest in the subjects who were scanned up to 12 h after receiving predoses of ziprasidone was more difficult in view of the extensive blockade of raclopride binding. For these subjects an additional "early" summated image was created from frames 2–14 of the dynamic raclopride scan. This image averaged activity for the first 5 min of the scanning procedure when the distribution of radioligand is determined primarily by cerebral blood flow, thereby giving additional anatomical information. For those subjects where there was clearly extensive blockade of raclopride binding the ROIs were positioned with reference to the "early" summated images and the standard raclopride summated images, and by thresholding the images to show the best possible definition between areas of differential ligand binding. Time activity curves were plotted for each region in each subject and the kinetics of brain ^{11}C-raclopride were modelled using the cerebellum as a reference tissue to derive an estimation of binding potential (BP), the ratio of the rate constants for binding to and dissociation from dopamine D_2 receptors (Hume et al. 1992; Bench et al. 1993). Binding potential data from nine normal male controls were available, including the placebo predosed subject from the present study. They had an age range of 26–72 years (mean 47±20). The controls were examined using identical methods and equipment over the preceding 2 years and their scans were analysed by the same investigator (C.J.B.).

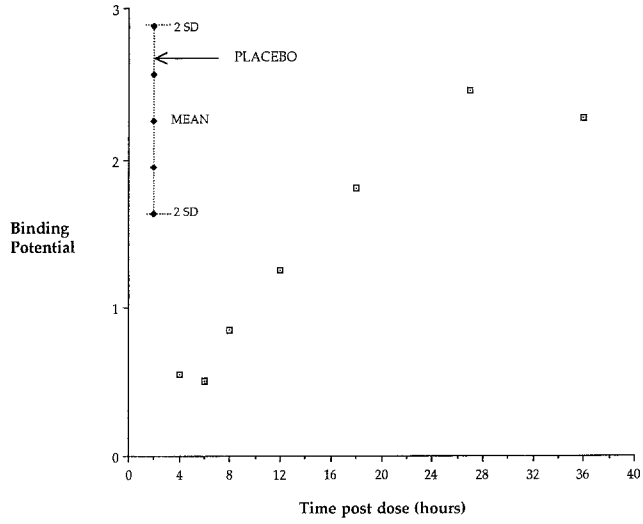

Fig. 1 Binding potential and time post dosing. The mean and range (2 SD) of binding potential from nine non-predosed normal control subjects is included. A data point has been included for the subject predosed with 40 mg ziprasidone and scanned at 5.75 h post-dose in the dose finding study previously reported (Bench et al. 1993)

Results

Binding potential

With increasing time between dosing and scanning there was increased uptake of ^{11}C-raclopride in the striatum, reflecting decremental central dopamine D_2 receptor blockade. Binding potential (BP) increased accordingly so that in the subjects scanned 18 h or more post-dose the BP was within the range (2.26±0.62, mean±2 SD) for BP obtained from the nine normal volunteers (Fig. 1). Binding potential had increased to above the mean normal value by 27 h post-dose.

Ziprasidone pharmacokinetics

The time course of the serum concentration for the subjects predosed with ziprasidone is shown in Fig. 2. The individual values for the area under the serum ziprasidone concentration-time curve from time 0 to 36 h post-dose (AUC[0–36]) are presented in Table 1. There were strong correlations between absolute values of ziprasidone at the time of PET scanning and binding potential (r=–0.96; P<0.0001), but not between AUC[0–36] and BP (r=0.57; P<0.18). Absolute values of ziprasidone at time of scanning also correlated with prolactin levels at the same time (r=0.89; P<0.02).

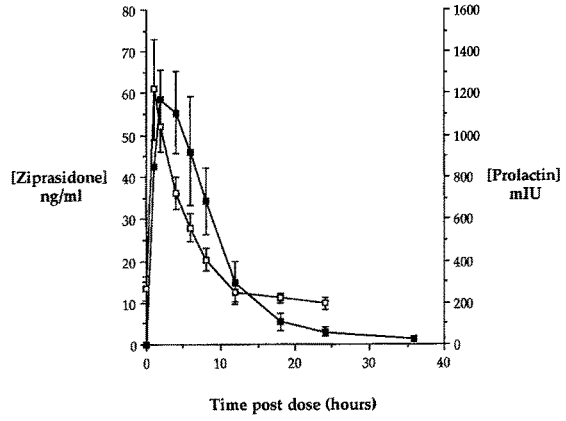

Fig. 2 Serum ziprasidone (*closed squares*) and prolactin levels (*open squares*) as a function of the time post dose. The values given are the means for seven subjects at each time point, including the subject predosed with 40 mg in the previous seven dose finding study (Bench et al. 1993). The *error bars* indicate the standard errors of the means (SEM)

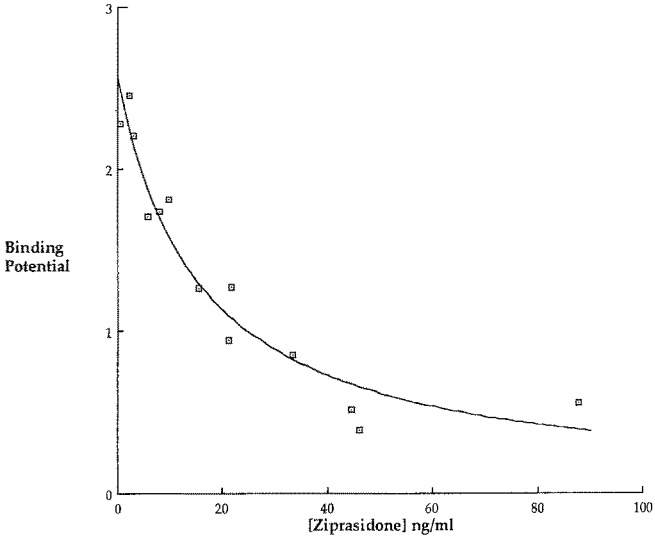

Fig. 3 Binding potential (*BP*) as a function of serum concentration of ziprasidone in 13 subjects. The relationship is curvilinear and the BP curve can be fitted directly according to the equation:

$$BP = \frac{B_{max'}}{K_{d'} + [\text{Ziprasidone}]}$$

where $B_{max'}$ and $K_{d'}$ are apparent B_{max} and K_d expressed interms of the serum concentration of ziprasidone rather than the free tissue concentration (which can not be measured with PET)

Prolactin response

Placebo predose failed to produce an increase in plasma PRL above baseline. The six subjects predosed with 40 mg ziprasidone all showed robust prolactin responses (Table 1). The time course of the prolactin response is shown in Fig. 2. There was a correlation between PRL at the time of PET scanning and binding potential (r=–0.89; P<0.02), but not between BP and the peak-baseline measure of the overall prolactin response (r=–0.43; P<0.34). Prolactin levels had returned to within the normal range in five out of six subjects by 12 h and in all subjects by 18 h.

Discussion

PET was used to calculate the binding potential of ^{11}C-raclopride in the striatum of 6 normal subjects at times between 4 and 36 h after taking a single oral dose of 40 mg of the novel neuroleptic ziprasidone. With increasing time post dose there was an increase in binding potential, indicating decreasing central dopamine D_2 receptor blockade. Binding potential correlated both with blood levels of ziprasidone and with plasma prolactin levels at the time of PET scanning.

The correlation of the concentration of ziprasidone at the time of scanning with the PET derived measure of binding potential (r=.-0.96, P<0.0001) was greater than that with the serum prolactin level at the time of scanning (r=-0.89, P<0.02). This suggests that binding potential is a more accurate index of D2 antagonism in the brain than neuroleptic-induced prolactin increases which are primarily an index of D2 antagonism at the pituitary level. Although binding potential (BP) correlated with the serum concentration of ziprasidone at the time of scanning it did not with the overall availability of ziprasidone as assessed by the AUC[0–36] (r=-0.57, P<0.18). In theory, intersubject differences in drug metabolism or disposition could affect the results of a study of this design in which the time course of central ziprasidone D2 binding is inferred from a single PET measurement in different subjects at different time points. Examination of the individual pharmacokinetic data showed there was a 2.8–4.5 fold variation in plasma levels among the subjects at each time point post-dose. The mean values for plasma levels and the standard errors of the means are presented for each time point in Fig. 2. In practice, we measured a smooth curvilinear decrease in ziprasidone concentrations and corresponding increase in binding potential with increasing time post-dose across subjects. While serum prolactin concentrations at the time of scanning correlated significantly with BP, the measure of overall prolactin response (peak-baseline) did not (r=-0.43, P<0.34).

A number of PET studies have now described in age related decrease in D2 receptors. This is an important consideration in the present study in which the controls are older than the subjects who received ziprasidone. Thus, Antonini et al. (1993) described a 0.6% decline in putaminal 11C-raclopride binding per year after approximately 30 years of age. For our control group this would result in an age corrected mean binding potential of 2.57±0.35 compared with the measured values of 2.26±0.31. With this higher reference value the time taken to return to the normal range (mean±2 SD) of binding potential would be increased by approximately 2 h to just over 18 h (Fig. 1).

Measurement of binding potential in the acute phase of medication could be underestimated due to the antagonism of D_2 autoreceptors and the consequent increase in extracellular dopamine concentrations (Zetterstom et al. 1984). In theory, this may lead to decreased measurement of brain radioactivity due to competition between increased levels of endogenous dopamine and ^{11}C-raclopride at the D_2 receptor (Bunney and Grace 1978; Chiodo and Bunney 1985). The present study was designed to examine binding potential at various times between 4 and 36 h post-dose. If there is a significant effect of acute dosage on intracellular dopamine concentration, and therefore binding of ^{11}Ca-raclopride, this would be expected to be maximal in the studies performed soon after dosing and therefore lead to greater underestimation of BP. However, Hume et al. (1992) have shown in the rat that dopamine levels need to be extensively raised by amphetamine to produce appreciable changes in raclopride binding and Farde et al. (1992) have suggested that amphetamine causes a maximum decrease in ^{11}C-raclopride binding of 16%. Since neuroleptic induced increases in dopamine are at most 2-fold (Zhang et al. 1989), this is unlikely to have a major effect on the results of this study.

The calculation of binding potential also assumes no effect of neuroleptic treatment on post-synaptic dopamine receptors in the striatum over the time course of the study. Whereas in the acute phase of medication antagonism of D_2 autoreceptors causes an increase in extracellular dopamine concentrations (Zetterstom et al. 1984), in the chronically medicated state animal models show upregulation (increased numbers) of dopamine D_2 receptors (Burt et al. 1977; Clow et al. 1980). Earlier PET studies of the effects of haloperidol and sulpiride suggested that levels of occupancy do not change substantially from acute to chronic dosage (Farde et al. 1988b, 1989). However, Farde et al. (1990) reported increased dopamine D_2 receptor density measured with PET in a patient 2 weeks after the withdrawal of sulpiride. In addition, Baron et al. (1989) found increased availability of D_2 receptors in two patients medicated for over 1 month after withdrawal of neuroleptics. This would suggest that in the chronically medicated state receptor occupancy is underestimated (therefore binding potential overestimated) by PET due to upregulation of D_2 receptors and if this is a dose-dependent effect then binding potential will be more overestimated in patients with high occupancy. The present study, in which we have inferred the time course of occupancy by measuring binding potential in normal volunteers after a single dosage of neuroleptic is unlikely to be confounded by the effects of upregulation.

It is likely that the time course of ziprasidone binding after withdrawal from chronic administration would be different from that observed in this study. The majority of studies which have studied the time course of occupancy after withdrawal of neuroleptics have done so in patients (rather than normal controls) who have been treated for long periods of time with either oral or depot medication. As discussed previously, interpretation of these results has to consider the effect of possible receptor upregulation. Some of these studies which have also examined the relationship between the PET measure of D_2 occupancy, plasma levels of neuroleptics and prolactin levels are considered below.

Using PET and ^{76}Br-bromospiperone in eight patients withdrawn from neuroleptics after 2 months' treatment, Cambon et al. (1987) found that receptor availability returned rapidly towards normal values, particularly in two patients on higher doses of neuroleptics before withdrawal. In these patients there was return to normal or near normal values for occupancy within 3 days. In an expansion of this study Baron et al. (1989) examined the relationships between D_2 occupancy and plasma prolactin in 16 patients after periods of drug withdrawal ranging from 1 day to 3 months. They found a sharp increase in available D_2 receptors to normal values within 5–12 days, and in two cases within 1–3 days. After neuroleptic withdrawal the PRL values showed an even more rapid decline, with all values being within the normal range within 3 days of withdrawal. There was a curvilinear relationship between the percentage decline in PRL and the increase in receptor occupancy (Baron et al. 1989).

Using PET and ^{18}F-*N* methylspiroperidol in schizophrenic patients, Smith et al. (1988) found that receptor availability returned to within the normal range between 60 and 156 h after stopping haloperidol. In contrast to Cambon et al. (1987), they established that the time taken to return to baseline receptor availability was increased in patients on higher doses of neuroleptics. Increase in receptor availability was directly related to HPD plasma levels and if expressed in terms of "occupancy" resembled a classical dose-response curve relating bound to free neuroleptic concentration. Farde et al. (1988b) established that significant D_2 occupancy was still present up to 27 h after withdrawal of neuroleptics, despite substantial reductions in serum levels. The authors proposed a curvilinear relationship between drug concentration and receptor occupancy which was confirmed in a further study in a patient treated with decreasing amounts of over a 9-week period.

In summary, although previous studies are not directly comparable either by virtue of the different patient groups studied, different neuroleptics used or differences in PET/tracer methodologies, and are potentially confounded by the effects of receptor upregulation, they all suggest that return to normal receptor availability (and neuroleptic washout) occurs between 24 and 156 h. The shorter "washout" times usually appear after relatively lower doses of neuroleptics. The present study finds that after single acute dosage in normal volunteers of 40 mg Ziprasidone, washout for the striatum, as indexed by a return to binding potential (BP) within the normal range (mean BP – 2 SD), is seen at 18 h. This relatively rapid washout of neuroleptics from their striatal binding sites is at variance with clinical data which demonstrates pro-

longed duration of action (Hershon et al. 1972), but is in keeping with reported neuroleptic clearance rates from plasma and brain tissue (Forsman and Ohman 1977; Itoh et al. 1984). The present study also adds to the evidence for a curvilinear relationship between neuroleptic concentrations and D_2 occupancy, in that at high blood concentrations of ziprasidone there is a relatively smaller decrease in binding potential (Fig. 3).

The previous PET study that examined serum prolactin systematically after withdrawal of neuroleptics described reduction to the normal range within 3 days as compared to 12–18 h in the present study (Baron et al. 1989). This may be an effect of chronic versus acute dosing. Both studies found that the time course of the decrease in prolactin was in advance of the decrease in the PET measure of receptor occupancy; elimination of neuroleptics from the pituitary, which is devoid of blood-brain barrier, may occur at a much faster rate than from the striatum.

In a previous dose finding study (Bench et al. 1993) it was demonstrated that a dose of 40 mg of ziprasidone in normal subjects decreased binding potential to 77% of the mean value in normal volunteers, an effect that is likely to be associated with antipsychotic efficacy (Cambon et al. 1987; Farde et al. 1988b). The present study shows that this reduction in binding potential is maintained for between 6 and 8 h post-dose, with a return to within 2 SD of the mean value at 18 h and to above the mean within 27 h. When considered with the standard pharmacokinetic data, this supports a twice-daily dosage regime. We have not examined the time course of occupancy after withdrawal from long term medication. Those studies which have (see above) show a that return to normal receptor availability occurs at between 24 and 156 h, with some evidence for a longer period to normal availability when higher doses of neuroleptics were administered prior to withdrawal.

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