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Continuous Intravenous Infusion of Iodine-123-IBZM for SPECT Determination of Human Brain Dopamine Receptor Occupancy by Antipsychotic Agent RWJ-37796

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PET has shown that dose-dependent in vivo occupancy of dopamine receptors by antipsychotic drugs is associated with clinical response to antipsychotic agents and the production of extrapyramidal side effects. We studied the feasibility of administering [^{123}I]IBZM as a bolus plus continuous infusion over 8 hr to achieve unchanging regional brain activity levels, and the application of [^{123}I]IBZM continuous infusion to examine the effects of the antipsychotic agent RWJ-37796, on striatal activity in humans. **Methods:** Five healthy male subjects received a bolus of [^{123}I]IBZM followed by a continuous infusion at a bolus (mCi):infusion (mCi/hr) ratio of 6:1. Serial SPECT images were obtained every 2–3 min for a total of 8 hr with a 1–2 hr break in the scanning session. Serial venous blood samples were obtained every 30 min for the duration of the study. All five subjects achieved unchanging plasma [^{123}I]IBZM and striatal brain-activity levels over the 300–420 min postinitiation of tracer infusion. Two subjects achieved flat brain time-activity curves later than the others, suggesting the bolus-to-infusion ratio was slightly high. An additional six healthy male subjects received a similar bolus plus constant infusion of [^{123}I]IBZM. RWJ-37796 (0.04 mg/kg) was administered intravenously 157 ± 13.7 min after the initiation of [^{123}I]IBZM infusion. Serial SPECT brain images, serum prolactin and extrapyramidal side effect ratings were obtained for an additional 330 min. **Results:** All six subjects demonstrated rapid and marked reduction of striatal activity following RWJ-37796 without return of striatal activity to baseline levels over the 5.5 hr of continued [^{123}I]IBZM administration. Estimated receptor occupancy by RWJ-37796 was 57% ± 5% (range 47%–67%). Prolactin was only transiently increased in all subjects by 1054% ± 1084% over baseline. One subject experienced moderate extrapyramidal symptoms (akasthisia) during RWJ-37796 injection. **Conclusion:** SPECT imaging during continuous [^{123}I]IBZM infusion provides a powerful within-scan method for determining both temporal binding characteristics and receptor occupancy of striatal dopamine receptors by antipsychotic agents.

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Dopamine D2 receptor blockade has been associated with both the antipsychotic efficacy of neuroleptic agents and extrapyramidal side effects (EPS). Functional brain imaging of dopamine receptors with PET has shown that 70%–89% dopamine D2 receptor blockade, by classical antipsychotic agents, is correlated with clinical response in schizophrenic patients, whereas extrapyramidal side effects are prominent at dopamine receptor occupancies greater than 74%–82% (*1*). These studies suggest a higher percentage of D2 receptor occupancy is required for the production of EPS than for clinical efficacy. Hence, in vivo demonstration of dopamine receptor occupancy by antipsychotic agents in humans may be helpful for directing medication dosing strategies in the development of antipsychotic agents for human use.

Current in vivo approaches for determining medication doses in antipsychotic drug development typically require behavioral studies of dose-dependent extrapyramidal motor system side effects in animals. In humans, the evaluation of antipsychotic-induced elevations of serum prolactin as a peripheral measure of central dopamine receptor occupancy or empirical assessment of side effect liability in early drug trials may be helpful in targeting a clinically-appropriate medication dose. These approaches are somewhat problematic in the developmental assessment of the so-called atypical antipsychotic agents, which have less potential for producing neurological side effects and may produce only transient elevation of serum prolactin.

In this context, application of SPECT imaging of dopamine D2 receptors using [^{123}I]iodobenzamide ([^{123}I]IBZM) could provide additional information about drug receptor occupancy.

The prolonged striatal uptake of [^{123}I]IBZM allows administration of displacing doses of antipsychotic drugs during dynamic brain imaging (*2*). In this algorithm, an antipsychotic drug administered after [^{123}I]IBZM injection competes for binding at the dopamine receptor to produce measureable displacement of radioactivity in regions of high receptor density. Thus, antipsychotic-induced washout of striatal activity can provide information about the time course of antipsychotic drug binding to dopamine receptors and the percent occupancy of dopamine receptors. Nonetheless, within-subject variability in striatal uptake, washout and peripheral clearance of [^{123}I]IBZM and relatively high nonspecific binding of [^{123}I]IBZM in the brain (*3,4*) decreases the sensitivity of [^{123}I]IBZM SPECT for estimating occupancy of dopamine receptors by antipsychotic agents in this fashion.

Between subject variability in brain uptake and washout of radiotracer could be reduced by administering [^{123}I]IBZM as a prolonged, continuous infusion. Under such conditions, we hypothesize that the rate of [^{123}I]IBZM association and dissociation from brain dopamine receptors equalizes and thus provides unchanging regional brain time-activity data for measuring the effects of subsequently administered displacing drugs. The first aim of this study was to determine the feasibility of injecting [^{123}I]IBZM as a bolus plus constant infusion in healthy human subjects during dynamic SPECT brain imaging.

RWJ-37796 is a structurally novel antipsychotic compound with selective binding to dopamine D2/D3, 5-HT_1, alpha$_1$ and alpha$_2$ receptors. Preclinical pharmacologic properties suggest the agent has low liability to produce extrapyramidal side effects and, thus, may be superior to standard antipsychotic agents in current use. Secondly, we used [^{123}I]IBZM as a constant infusion method in healthy human subjects for evaluating the time course and quantitation of receptor occupancy following injection of RWJ-37796.

MATERIALS AND METHODS

Study 1: Continuous Infusion of Iodine-123-IBZM

Five healthy male subjects with no history of neurological or psychiatric illness (age = 22.7 ± 0.5 yr, weight = 79.5 ± 10.0 kg) provided informed consent. Data are expressed as mean ± s.d. All subjects had normal physical and mental status examination, serum chemistries, blood counts, thyroid indices, urinalysis and urine drug screen obtained prior to participation in the study. Subjects received saturated potassium iodide (400 mg) in three doses over the 12 hr before injection of radiotracer.

Each subject participated in a single SPECT scan with [^{123}I]IBZM prepared and purified according to previously described methods (*2*). Tracer was administered as an intravenous bolus over 5–10 sec followed by a constant infusion at a ratio of 6:1 [bolus (mCi) infusion rate (mCi/hr) total dose 496 ± 89 MBq (13.4 ± 2.4 mCi). The ratio was determined on the basis of computer simulations of human pharmacokinetic data described previously (*2*). For these simulations, bolus injection data from humans previously studied with [^{123}I]IBZM SPECT were analyzed using MATLAB (The Mathworks, Natick, MA) implemented on the Macintosh Quadra 950 computer (Apple Computer, Cupertino, CA). Using the calculated peripheral clearance determined in arterial plasma and measured brain uptakes, the program modeled the regional brain time-activity curves resulting from variation of the bolus (mCi):constant infusion (mCi/hr) ratio of [^{123}I]IBZM. For the bolus human studies modeled in this fashion, the ratio of 6:1 achieved plateau earlier than other modeled ratios.

Subjects were positioned in the camera with a fixed light source oriented along the canthomeatal line. After locating the slice demonstrating best visualization of striatum, as previously described (*2*), serial SPECT scans were performed every 2–3 min on the 810X Brain Imager (Strichman Medical Equipment, Medfield, MA), a high sensitivity, single-slice SPECT device. Subjects were imaged for a total of 8 hr postinitiation of tracer infusion. All subjects were removed from the camera after the initial 3–4 hr of imaging for a 1-hr break, repositioned in the camera and imaged for the remaining time up to 8-hr. In order to demonstrate the effects of overshooting the bolus:constant infusion ratio, one subject had an additional SPECT scan during administration of [^{123}I]IBZM at a ratio of 9:1.

Reconstructed images were attenuation-corrected using a Chang zero order correction by application of an ellipse drawn around the brain assuming uniform attenuation equal to water. A region of interest (ROI) template, including the left and right striatum, frontal, and occipital cortices, was created based on visual identification of striata and applied to all images in the study. The density of counts (expressed in units of counts/pixel/min) were obtained for each ROI and decay-corrected to the time of injection.

Serial venous blood samples were obtained in all subjects every 30 min after initiation of [^{123}I]IBZM infusion for the duration of the scan. Plasma was separated from whole blood and extracted with ethyl acetate. The ethyl acetate extractable component was analyzed for plasma parent and free parent plasma concentration using reverse phase HPLC according to previously described methods (*2*). Plasma data were decay-corrected to the time of injection.

Study 2: RWJ-37796 Administration During SPECT Imaging

Six additional healthy male subjects (age 27.0 ± 10.6 yr; weight 73.7 ± 6.7 kg) provided informed consent following the health screening evaluations described for Study 1. All subjects received a bolus plus continuous infusion of [^{123}I]IBZM at a ratio of 6:1 (total injected dose 529 ± 67 MBq (14.3 ± 1.8 mCi)). Serial images were acquired on the 810X Brain Imager following the protocol described above for localizing the slice with the highest striatal counts. RWJ-37796 (0.04 mg/kg i.v.) was administered over 30 min at 157 ± 13.7 min postinitiation of [^{123}I]IBZM infusion and serial 2-min images were obtained for an additional 330 min.

The Barnes Akasthisia Scale (*5*) and Simpson-Angus Scale of extrapyramidal symptoms (*6*) were obtained at baseline and then every 30–60 min following RWJ-37796 injection for the duration of the study.

Blood samples were procured every 30 min for determination of plasma prolactin levels. Plasma prolactin was measured by radioimmunoassay (Serono Diagnostics, Inc., Norwell, MA). Interassay and intra-assay coefficients of variation were 3% and 7%, respectively.

Images were attenuation- and decay-corrected as described in Study 1 and analyzed using the same ROI template to determine activity corresponding to left and right striatum, occipital and frontal cortices. Counts representing [^{123}I]IBZM binding to striatal dopamine receptors was estimated by assuming equivalence between striatal and occipital nonspecific and free activity and subtracting the occipital count density from total striatal activity. Percent receptor occupancy of RWJ-37796 was calculated from the percent change of this operationally-defined specific activity at the end of the study from the immediate pre-antipsychotic infusion level according to the following equation:

$$\% \text{ Occupancy by RWJ-37796 in striatum} = 100 - \frac{(\text{specific striatal activity after RWJ37796})}{(\text{specific striatal activity before RWJ37796})} \cdot \quad \text{Eq. 1}$$

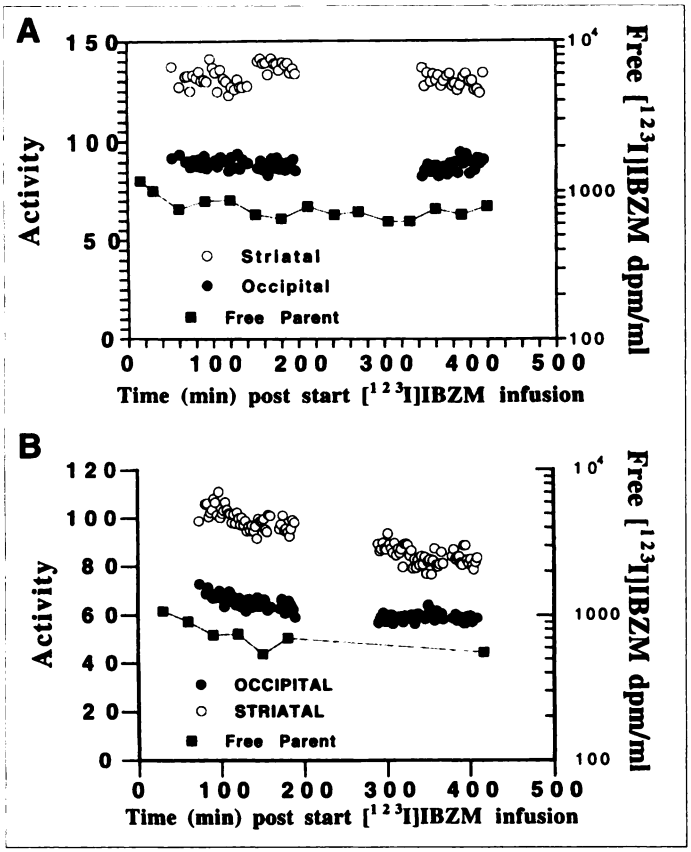

FIGURE 1. Time-activity data and free plasma [^{123}I]IBZM in two subjects in Study 1 receiving continuous infusion of tracer. Both subjects received [^{123}I]IBZM bolus (mCi):continuous infusion (mCi/hr) ratio of 6:1. (A) Subject shows rapid achievement of flat time-activity curve. (B) Subject demonstrates more prolonged time to achieve a flat curve, suggesting the ratio was too high for this subject.

RESULTS

Study 1

Plasma Iodine-123-IBZM Measures. Peak plasma levels of total and free [^{123}I]IBZM occurred in the first test sample, which was obtained 30 min after initiation of [^{123}I]IBZM infusion. Levels of total and free plasma parent compound achieved ±20% of the final value by 163 ± 98 min after initiation of tracer infusion in all subjects. Among the five subjects, the earliest time to achieve ±20% of final plasma value was 60 min (range 60–305 min).

SPECT Imaging. All subjects achieved stable, unchanging time-activity curves in striatum and occipital cortex (Fig. 1). Occipital cortex was within ±20% of the final value earlier (58.0 ± 16.9 min postinfusion initiation) than striatum (76.5 ± 24.8 min). Two subjects demonstrated prolonged time to reach unchanging striatal activity levels due to an apparent bolus overshoot (i.e., bolus:infusion ratio was too high).

A least squares linear fitting of the striatal activity for the 300–420 min time period demonstrated activity changes of −5.7% to +5.4% per hr (Table 1). Ratios of total striatal activity to occipital cortex activity during this time were 1.29–1.59 (Table 1).

The subject receiving the additional SPECT study at a ratio of 9:1 showed a high initial peak of striatal activity without achievment of stability over the 7 hr of infusion. Washout rates determined over the interval of 300–420 min were 208% higher for the subject compared to his other study at a 6:1 bolus: continuous infusion ratio.

TABLE 1
Study 1: Post-IBZM Infusion (300–420 min)

Subject no.	Percent washout per hr		Striatum:Occipital cortex ratio
	Striatal	Occipital	
1	−0.1	1.6	1.29
2	5.4	1.5	1.56
3	4.4	8.5	1.59
4	−3.0	−0.1	1.42
5	−5.7	7.1	1.48
Mean ± s.d.	0.2 ± 4.7	3.7 ± 3.8	1.47 ± 0.12

Study 2

Plasma Prolactin Measures. Prolactin levels were transiently increased to 1054% ± 1084% of baseline (range 239%–2744%) following RWJ-387796 infusion. Time-to-peak prolactin was 78 ± 45 min (Table 2) with a mean postpeak $T_{1/2}$ = 74 min (Fig. 3) for a monexponential fit of the data.

Motor Ratings. Five of the six subjects reported no side effects following RWJ-37796 injection. One subject experienced subjective sense of restlessness beginning 15 min after initiation of RWJ-37796 infusion and continuing for 60 min after completion of drug infusion. The peak total Barnes score was 4 (out of 5, consistent with severe akasthisia), occurring at 30 min postinitiation of RWJ-37796 infusion. The Simpson-Angus ratings increased from a score of 0 (no detectable EPS) at baseline to 3 (multiple limbs affected) at the 30-min RWJ-37796 time point. The remaining subjects showed no changes from baseline ratings of extrapyramidal side effects, akasthisia, dystonias or dyskinesias following RWJ-37796 administration.

SPECT Imaging. All subjects exhibited rapid reduction in striatal counts following the RWJ-37796 administration. Washout data fit to a monoexponetial curve demonstrated a mean $T_{1/2}$ = 42 ± 7.5 min. There were no effects of RWJ-37796 on occipital time-activity data in any subject (Fig. 2). One subject did not complete the study secondary to apparent drug-induced akathisia.

Predrug striatal specific activity was taken as the mean of specific binding estimates over the 20 min prior to RWJ-37796 infusion, while post RWJ-37796 determinations of specific striatal binding included the terminal 20 min of the experiment, beginning 153 ± 10.4 min after administration of RWJ-37796. This latter time represented 3.8 half-lives of the mean RWJ-37796-induced specific striatal activity washout from the six

TABLE 2
Study 2: Effects of RWJ-37796 (0.04 mg/kg i.v.)

Subject no.	Specific striatal activity		Peak prolactin increase (%baseline)
	Washout $T_{1/2}$ (min)	%Receptor occupancy	
6	46	47	239
7	31	58	320
8	45	60	349
9	52	54	576
10	43	67	2744
11*	37		2097
Mean ± s.d.	42 ± 7.5	57 ± 7.5	1054 ± 1083.7

*Subject 11 terminated the study early due to extrapyramidal side effects; the percent receptor occupancy was not estimated.

subjects. Specific brain activity was reduced to a mean 43% of baseline for an estimated receptor occupancy of 57% ± 5%, range 47%–67% (Table 2). There were no increases in striatal uptake over the additional 5.5 hr of study in five subjects despite continued infusion of [^{123}I]IBZM.

DISCUSSION

This study demonstrates the feasibility of an intravenous bolus plus constant infusion of [^{123}I]IBZM in humans to establish a steady-state plasma level and unchanging regional brain activity against which antipsychotic drugs may be administered. Administration of [^{123}I]IBZM as a constant infusion produces a state of equilibrium tracer binding. An equilibrium may be either a true or transient equilibrium. True equilibrium, also called "peak equilibrium" (*7*), occurs at the time of peak specific uptake, when the differential of the specific activity curve relative to time is zero (*8*). This is the most common use of the term "equilibrium." Transient equilibrium (*9*) is also referred to as a constant ratio, secular equilibrium (*8,10*), or pseudoequilibrium (*11*) and indicates a constant ratio of tissue-to-plasma or target-to-background regions within an organ (*12*).

What type of "equilibrium" is established during bolus plus constant infusion of [^{123}I]IBZM? The body as a whole may be considered at a steady state in which the rate of tracer delivery equals the rate of clearance of parent tracer from the plasma. This steady state thus provides a constant level of parent tracer in plasma, although total plasma activity is increasing due to the accumulation of radiometabolites. The continuous infusion results in stable levels of total striatal activity, total occipital activity, and specific striatal uptake in the brain.

Levels of parent tracer and total radioactivity are believed constant in brain in contrast to plasma. The difference between brain and plasma with regard to levels of total activity is due to the fact that radiolabeled metabolites of [^{123}I]IBZM are thought not to cross the blood-brain barrier. Thus, the terms "true equilibrium" and "constant ratio" would both apply to the brain. The difference between the true equilibrium (as defined by the differential of the specific activity curve relative to time) is that during constant infusion this condition is not instantaneous, but rather, represents a prolonged state of true equilibrium.

The homogenate binding literature describes an equilibrium as a dynamic and reversible state in which the rate of ligand association equals its rate of dissociation (*13*). This definition may also apply to the present studies as the binding of [^{123}I]IBZM is reversible in both human and nonhuman primates—as demonstrated by displacement of activity by RWJ-37796 or other dopaminergic agents (*2,4*).

The stability of the striatal time-activity curve over time is acceptable for drug displacement studies addressing the problem in bolus injections of distinguishing the displacing effects of drugs from the variable native washout of radiotracer from brain regions. Thus, the advantages of the equilibrium method include:

1. A stable baseline against which to assess the effects of displacing agent.
2. Baseline and displaced conditions are measured within one scanning session.
3. Results are independent of blood flow and effects of variable delivery of tracer to brain associated with heterogenous patterns of flow.
4. If entry of displacer is the time-limiting step in the decrease of activity of brain, then the time-activity curve provides pharmacokinetic information of displacing drug uptake in brain.
5. If the study is continued long enough, it would be possible to measure the rate of washout of the displacer from the brain.

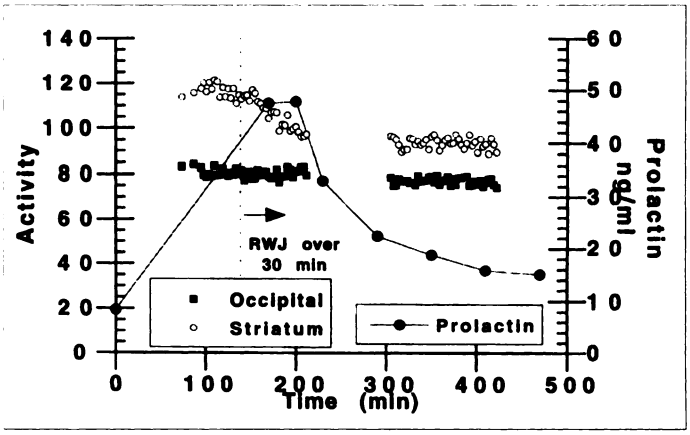

FIGURE 2. Time-activity data and plasma prolactin determination in subject receiving RWJ-37796 (0.04 mg/kg i.v. over 30 min) during continuous infusion of [^{123}I]IBZM. RWJ-37796 produces marked washout of total striatal activity to a plateau without effecting occipital activity. Prolactin is markedly but transiently elevated following RWJ-37796 administration.

In Study 1, both plasma parent activity and brain activity were within ±20% of the final value by 163 min, although striatal activity achieved this by approximately 76 min after initiation of tracer infusion. The fact that plasma activity was within this range later than brain may be a reflection of the statistical variation associated with our method for determining free parent compound. In other studies with a bolus plus constant infusion paradigm in humans using [^{123}I]iomazenil, plasma levels achieve stability prior to regional brain activity (*14*). Of the five subjects in this study receiving the 6:1 bolus:infusion ratio, two subjects had apparent overshoot, one subject demonstrated undershoot, while two subjects achieved a plateau of striatal time activity quickly. In all cases, the prolonged infusion permitted achievement of plateau. Optimizing the bolus:continuous infusion ratio for each individual may be useful for minimizing the time required to attain plateau, although this requires an additional SPECT study.

The striatal-to-occipital ratio over the flat portion of the

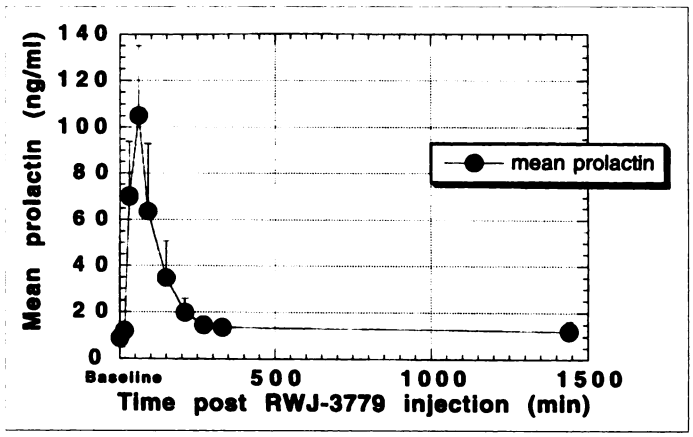

FIGURE 3. Mean prolactin elevations following RWJ-37796 infusion in six healthy Study 2 subjects.

time-activity curve is lower than the peak total striatal:occipital ratios from single bolus infusion studies (*2*). This is expected, for during a bolus injection, striatal:occipital ratios continue to increase over time as extrastriatal brain activity washes out faster than striatum.

The in vivo estimation of receptor occupancy in human subjects may be useful in developing dosing strategies for neuroleptic agents. Functional imaging studies of dopamine receptors using PET and [^{11}C]raclopride suggest that clinical doses of typical neuroleptic agents are associated with 70%–89% dopamine receptor occupancy and newer atypical antipsychotic agents like clozapine may produce therapeutic benefit at lower striatal dopamine receptor occupancy rates (*15,16*). This may explain the reduced tendency of clozapine to produce extrapyramidal side effects compared with standard neuroleptics. Antipsychotic agents with lower tendency to produce extrapyramidal side effects are more difficult to evaluate for human dose ranges using standard animal models like drug thresholds for producing catalepsy. In this regard, functional imaging may provide a useful in vivo method for estimating antipsychotic doses in humans. In distinction to homogenate binding methods, in vivo studies of receptor occupancy provide a measure of total occupancy by a drug and any reactive metabolites, appropriately weighted for penetration across the blood-brain barrier.

One source of error in the determination of dopamine receptor occupancy in the present investigation is the possibility that unchanging regional brain activity levels were not achieved at the time RWJ-37796 was administered. This would lower the calculated percent receptor occupancy in cases of undershooting the ratio, and increase the estimated binding in instances of overshooting the ratio. The present ratio of 6:1 was adequate for demonstrating the feasibility of this preliminary data, but issues of individual variability based on differences in the rate of peripheral clearance or demographic features (gender, age) in the selection of the best bolus:infusion ratio warrant further investigation. Nonetheless, comparison of the present calculated receptor occupancy (57%) for this dose of RWJ-37796 to studies conducted with PET and [^{11}C]raclopride produced identical estimates of binding (*17*).

The continuous infusion method also provides temporal information about antipsychotic binding to dopamine receptors both with regard to the rate of incorporation of drug onto receptors and the duration of drug binding. This study showed prolonged occupancy of dopamine receptors, even in the face of transient alterations in plasma prolactin levels. While it may be possible to monitor the time course of drug binding to the dopamine receptor, prolonged binding of many neuroleptic agents limits the logistical feasibility of determining dissociation of drug from receptors using this method.

CONCLUSION

The administration of [^{123}I]IBZM as a bolus plus constant infusion provides an unchanging striatal time-activity curve which suggests a state of prolonged equilibrium at the dopamine receptor. This provides a stable baseline against which dopamine receptor agents may be administered for characterization of percent receptor occupancy and temporal binding characteristics.

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