THE EFFECT OF RATE OF DRUG ADMINISTRATION ON THE EXTENT AND TIME COURSE OF PHENCYCLIDINE DISTRIBUTION IN RAT BRAIN, TESTIS, AND SERUM

JOEL W. PROKSCH,1 W. BROOKS GENTRY, AND S. MICHAEL OWENS

Departments of Pharmacology and Toxicology (J.W.P., W.B.G., S.M.O.) and Anesthesiology (W.B.G.), College of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas

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ABSTRACT:

The goal of these studies was to examine the relationship between the rate of phencyclidine (PCP) administration and PCP tissue distribution. The time course of PCP distribution in serum, brain, and testis after rapid (i.v.) and slow (s.c.) administration was studied. Brain and serum PCP concentrations after an i.v. bolus dose (1 mg/kg at 900 μg/min) were highest at 30 s and decreased biphaseically, with serum concentrations decreasing 30 times faster than brain concentrations during the early phase. Consequently, the brain-to-serum PCP concentration ratio increased from 8:1 at 30 s to 14:1 at 20 min before equilibrating at a ratio of 3:1 that remained constant from 1 to 8 h. In contrast, the testis-to-serum ratio increased slowly from 1:1 to 12:1 over 4 h, and then remained constant. In a separate group of animals, an s.c. infusion of PCP (18 mg/kg/day or 3.6 μg/min) produced a brain-to-serum ratio (6:1) that remained constant throughout the 96-h infusion. Testis-to-serum ratios increased from 4:1 at 1 h to 12:1 at 8 h and then remained constant for 96 h. Steady-state infusion of a pharmacologically inactive dose (2.5 mg/kg/day) produced a brain-to-serum ratio (3:1) that was significantly lower than the ratio (6:1) after infusion of the three pharmacologically active doses (10–25 mg/kg/day). The temporary high brain PCP concentrations and the dynamic disequilibrium between brain and serum concentrations after rapid i.v. administration could provide a better understanding of the preference of the human drug abuser for rapid rates (e.g., i.v. or smoking) of drug administration.

A number of reports indicate a link between the rate of entry of drugs of abuse into the brain and the addiction potential of those drugs (e.g., Russell and Feyerabend, 1978; Verebey and Godl, 1988; Henningfield and Keenan, 1993). In general, drugs tend to be less addicting if their onset of activity is slow and the duration of action is long. For example, the addiction potential of i.v. cocaine use is greater than intranasal use, which is greater than oral use (Verebey and Godl, 1988). Blood cocaine concentration-versus-time profiles are remarkably different for these three routes of administration, with the i.v. route resulting in the most rapid increase in concentrations, and the highest peak brain concentrations (Verebey and Godl, 1988). This potential pharmacokinetic/pharmacodynamic link [i.e., rapid rises in phencyclidine (PCP) concentrations result in rapid onset of pharmacologic effects] appears to be related to the preference of many drug addicts for administering drugs by rapid i.v. or smoking routes of administration rather than slower intranasal, oral, or i.m. routes. A similar link is found when examining the addiction potential of nicotine (Henningfield and Keenan, 1993). Thus, nicotine delivery devices used in smoking cessation programs (e.g., polacrilex gum or transdermal patches) may ameliorate the addiction potential by providing a slow and continuous drug delivery, unlike the rapid surges in nicotine concentrations produced by smoking a cigarette (Schneider et al., 1996). Consequently, these replacement therapies appear to suppress the symptoms of nicotine withdrawal, while minimizing the reinforcing subjective effects (e.g., surges or rushes in effects) associated with a rapid bolus effect from smoking the drug (O’Brien, 1996).

The addiction or abuse potential of PCP also appears to be influenced by the rate at which the drug is administered (Zukin et al., 1997). Previous studies show that the onset of PCP effects is rapid after i.v. administration to rats, suggesting that PCP quickly enters the central nervous system (Valentine and Owens, 1996; Hardin et al., 1998). Although brain concentrations should change rapidly as a result of changes in blood concentrations, several reports suggest that plasma PCP concentrations may not accurately reflect drug concentrations in the brain. Martin et al. (1980) observed that the brain-to-plasma PCP concentration ratio in mice was not constant with time after drug administration. In addition, postmortem analysis of PCP concentrations in humans also shows an inconsistent relationship between serum and tissue PCP concentrations (Burns and Lerner, 1976; Reynolds, 1976; Bailey, 1979). However, the mechanism and time course of this underappreciated (and not easily predicted) difference between brain and serum concentrations is unclear. Indeed, the relationship is complex and likely dependent on multiple factors like
the equilibrium between drug uptake and efflux, tissue binding, cellular trapping, and metabolism. Also, the tissue sampling protocols were not designed to fully describe the complete time course of PCP distribution in the brain.

The purpose of these studies was to examine the effect of PCP dose and the rate of administration on the time course and extent of PCP distribution into the brain and testis. An i.v. bolus and s.c. infusion to steady-state were used to represent the extremes of a very rapid (i.e., 900 μg/min) and a very slow (i.e., 0.5–5 μg/min) rate of drug input. Brain, testis, and serum concentration-versus-time profiles were determined, and these data were used to examine the relationships among brain, serum, and testis PCP concentrations over time. Testis concentrations were studied as a control tissue for the brain because the testis has a blood-tissue barrier that is similar in function to the blood-brain barrier. In addition, the brain, serum, and testis PCP concentrations were measured at steady state over a 10-fold range of s.c. infusion doses to help determine the relationship between PCP dose and PCP tissue partitioning.

Materials and Methods

Drugs and Chemicals. [3H]PCP (1-(1-phenyl-1H[1]cyclohexyl)piperidine) and PCP HCl (1-(1-phenylcyclohexyl)piperidine hydrochloride) were obtained from the National Institute on Drug Abuse (Rockville, MD). The [3H]PCP (15.3 Ci/mmol) was used as a radioligand in a radioimmunoassay (RIA) for determining PCP concentrations in serum and to determine analytical recoveries after extraction of PCP from tissues. All PCP concentrations were calculated as the free base. Sodium sulfate, sodium azide, and BSA were purchased from Sigma Chemical Company (St. Louis, MO). All other chemicals were obtained from Fisher Scientific (Springfield, NJ), unless otherwise stated.

Animals. Adult male Sprague-Dawley rats (270–300 g) were purchased from Hilltop Laboratory Animals, Inc. (Scottsdale, PA). Animals for the i.v. PCP experiments were purchased with an indwelling jugular venous cannula (Dow Corning silastic tubing, 0.020-inch inside diameter; 0.037-inch outside diameter) in the right external jugular vein. Before shipping, the cannula was placed in the subdermal space for protection during shipping. On arrival, each cannula was removed from the subdermal space and kept patent with heparinized saline (25 U every other day). Animals were allowed at least 1 week for acclimation to their new environment before use. Each animal was fed a controlled diet on a daily basis to maintain its body weight at approximately 300 g. All animal experiments in these studies were carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health.

Protocol for Pharmacokinetic Studies with an Acute i.v. Bolus Dose. All rats (n = 3–4 per time point) received PCP (1 mg/kg) as an i.v. bolus dose administered over 20 s into the right jugular vein through an indwelling cannula. The volume of the injection was 1.0 ml/kg, and the cannula was flushed with 0.3 ml of saline after PCP administration to ensure complete delivery of drug. This dose of PCP was chosen after consideration of the behavioral effects in the rat (Valentine and Owens, 1996; Valentine and Owens, 1996) and human use patterns (Zukin et al., 1997). We have previously calculated that approximately 90% of human PCP overdoses resulting in emergency room visits within the working range of the assay (i.e., 2–100 ng/ml). PCP standards were purchased from Sigma Chemical Company (St. Louis, MO). All other chemicals were obtained from Fisher Scientific (Springfield, NJ), unless otherwise stated.

Analysis of Biological Samples. PCP concentrations in serum and tissues were calculated as previously described (Valentine and Owens, 1996) with minor modifications. The specificity, accuracy, and reproducibility of this assay has been extensively validated (Owens et al., 1982, 1987; Owens, 1985; Valentine and Owens, 1996). PCP concentrations in tissue samples were determined by RIA after extracting the PCP from the sample. Tissue samples were homogenized in four volumes of ice-cold distilled water using an SDT Tissumizer (Tekmar Company, Cincinnati, OH). Aliquots (300-μl) from the homogenized samples were extracted with 150 μl of N NaOH and extracted twice with 500 μl of hexane for 1 h. The samples were then back-extracted into water by adding 300 μl of 0.1 N HCl to the combined hexane fractions and mixing for 1 h. The aqueous layer was then alkalized with 150 μl of 2 N NaOH after discarding the hexane layer, and again extracted with 500 μl of hexane. The hexane fractions were transferred to a siliconized test tube, brought to dryness by vacuum centrifugation, and resuspended in 300 μl of normal, drug-free sheep serum. PCP extraction efficiency was determined with blank testis and brain homogenates spiked with a known amount of [3H]PCP and extracted along with samples for RIA analysis. After resuspending the spiked controls in drug-free sheep serum, the percentage of recovery was calculated from liquid scintillation spectrometry analysis of the radioactivity in each specimen.

Protocol for Pharmacokinetic Studies with a Chronic s.c. Infusion Dose. PCP was infused at 2.5, 10, 18, or 25 mg/kg/day by s.c. osmotic 7-day minipumps (model 2 ML1; Alza Corp., Palo Alto, CA). Osmotic minipumps were implanted s.c. on the back of rats anesthetized with ether. Before implantation, the minipumps were filled with PCP dissolved in sterile saline (2 ml per pump). The pumps delivered approximately 10.0 μl/day of the appropriate dose for the duration of the experiment. A s.c. infusion to steady state was chosen because it produces a serum PCP concentration-time profile and a pharmacokinetic profile in rats that is essentially identical with an i.v. infusion to steady state (Wessinger and Owens, 1991a). However, an s.c. infusion is easier to maintain over extended time periods than an i.v. infusion. The doses used in this study were chosen to cover a full range of behavioral effects, from no behavioral effects produced at the lowest dose (2.5 mg/kg/day) to almost continuous locomotor activity and ataxia for several days produced at the highest dose (25 mg/kg/day). We also chose these doses based on the knowledge of the operant behavioral effects of similar PCP infusion rates in rats (Wessinger and Owens, 1991b). This previous study shows that infusions of PCP greater than 5 mg/kg/day are required to produce significant behavioral effects in male rats.

To study the time course of PCP distribution in tissues, animals (n = 3 per time point) received an 18 mg/kg/day infusion of PCP. Blood, brain, and testis samples were collected at 1, 8, 24, 48, or 96 h after implantation of the s.c. osmotic minipumps. Because the terminal elimination half-life (t1/2) of PCP is about 4 h in the rat (Wessinger and Owens, 1991a), steady-state concentrations were achieved in approximately 16 to 28 h (or 4–7 t1/2).

To study the effects of PCP dose on tissue distribution, four infusion doses were used and samples were collected at a single steady-state time point. Animals received 2.5, 10, 18, or 25 mg/kg/day (n = 4 per dose) and blood, brain, and testis were collected 24 h after pump implantation.

Analysis of Pharmacokinetic Data. Concentration-versus-time data was performed using model-dependent methods. At each sample time point, the average PCP concentration from three to four rats was used for pharmacokinetic analysis. All pharmacokinetic analyses were performed using the computer software package WinNonlin (Scientific Consulting, Inc., Cary, NC). A nonlinear regression curve was fitted to the serum and tissue PCP concentration-time data. The best-fit curve was chosen

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after fitting monoexponential, biexponential, and triexponential curves to the data using both 1/\(^2\) and 1/y\(^2\) weighting functions. The selection of the best-fit curve for each data set was based on visual comparison of the fits, the statistical variance of the pharmacokinetic parameters, analysis of the residuals plot, and a statistical F ratio test as described by Boxenbaum et al. (1974).

Calculations included determination of the terminal elimination rate constant, the \(t_{1/2}\) of PCP into the testis; \(t_{1/2Z}\), the distribution \(t_{1/2}\) of PCP from brain and serum; \(C_{\text{max}}\) and \(T_{\text{max}}\), maximum testis PCP concentration, and the time to maximum testis concentration, respectively; \(V_{\text{SS}}\), volume of distribution at steady state; AUC, area under the concentration-time curve; \(C_0\), initial serum or brain concentration.

### Statistical Analysis
All values are reported as the mean ± S.D. All statistical analyses were conducted using the computer software package SigmaStat (Jandel Corporation, San Rafael, CA). A one-way ANOVA followed by a Student-Neuman-Keuls post hoc test was used to compare differences among groups receiving different infusion doses of PCP. Statistical significance was considered to be achieved at a level of \(P < .05\).

### Results

**General Experimental Observations.** PCP administration, including implantation of s.c. osmotic minipumps, was well tolerated in all animals. Although we did not attempt to quantify behavioral effects in the current studies, PCP-induced effects appeared to be similar to results from previous studies (Wessinger and Owens, 1991b; Valentine et al., 1996; Hardin et al., 1998). For instance, the PCP-induced behavioral effects produced by the 1 mg/kg i.v. bolus dose included head weaving, ataxia, and hyperlocomotion that lasted for about 45 min, which were similar to the results of Valentine et al. (1996) and Hardin et al. (1998). Infusions (s.c.) of 10, 18, and 25 mg/kg/day produced dose-dependent effects similar to the results of Wessinger and Owens (1991b), which lasted for the first 1 to 3 days of s.c. infusions. As expected, no PCP-induced behavioral effects were observed at any time during infusion of the lowest s.c. PCP dose (2.5 mg/kg/day).

We also found that the calculated pharmacokinetic parameters in this study were consistent between the i.v. and s.c. groups. For instance, the PCP \(CL_S\) values for rats receiving the 1 mg/kg i.v. dose was 68 ml/min/kg (Table 1; model-dependent methods). The \(CL_S\) value for rats receiving the 18 mg/kg/day s.c. dose was 70 ml/min/kg (assuming a steady-state concentration of 178 ng/ml). These findings are consistent with findings for PCP administered both via i.v. and s.c. routes in previous studies from this laboratory (e.g., Wessinger and Owens, 1991a; Valentine and Owens, 1996; Proksch et al., 1998, 2000). In addition, \(CL_S\) values for the 2.5, 10, and 25 mg/kg/day doses were 55, 78, and 75 ml/min/kg.

For these studies, we first measured whole tissue concentrations, and then subtracted out the amount of drug in the blood content in the tissue based on inferior vena cava venous concentrations. This allowed a more accurate determination of the true tissue (without blood) concentrations.

**Tissue Distribution of PCP after Rapid i.v. Administration.** Serum and brain PCP concentrations were highest at the first measured time point (30 s) after a 20-s bolus i.v. injection (Fig. 1). In contrast, testis PCP concentrations reached a maximum value about 12 min after the i.v. injection, but sustained this level for approximately 1.5 h (Fig. 2). Results from model-dependent analysis of serum and tissue PCP concentration-time data are shown in Table 1. Serum and brain PCP concentration-time data were best described by a biexponential function with 1/y\(^2\) weighting. Testis PCP concentration-time data were best described by a monoexponential function with 1/y\(^2\) weighting and a first-order drug input.

Analysis of the tissue-to-serum PCP concentration ratios for brain and testis showed substantially different patterns (Figs. 1 and 2). At 30 s after PCP administration, brain PCP concentrations were already 8 times higher than serum concentrations. The brain-to-serum ratio continued to increase and peaked at approximately 14:1 within the first 20 min. Within 1 h, the brain-to-serum ratio decreased to a constant value of 3:1, which was sustained for the duration of the 8-h sampling period (Fig. 1, inset). In contrast, testis PCP concentrations were slower to equilibrate with serum PCP concentrations (Fig. 2, inset). The testis-to-serum ratio was 1:1 at 30 s after PCP administration, and slowly increased over several hours to a value of approximately 14:1. Despite the substantially slower rate of equilibration in the testis, concentrations in this organ eventually exceeded those in the brain by about 5-fold. These data for PCP concentrations in the normal rat brain, testis, and serum are consistent with the PCP concentration values for normal rats in a previous study of the effects of antibodies (both anti-PCP Fab and anti-PCP IgG) on PCP redistribution from tissues (Proksch et al., 2000).

**Time to PCP Steady-State during s.c. Infusion.** Figure 3 shows serum, brain, and testis concentrations throughout a 96-h infusion of 18 mg/kg/day PCP. Despite the high PCP concentrations in brain and testis, less than 0.5% of the total dose was present in either of these tissues at steady state. The testis-to-serum PCP concentration ratio over time showed a similar profile to the ratios produced by the bolus i.v. administration of PCP, with the ratio increasing over several hours to a value of approximately 14:1 (Fig. 4). In contrast, analysis of the brain-to-serum PCP concentration ratio showed a markedly different profile from the i.v. bolus data, with a constant value (5.8 ± 0.8) sustained for the duration of the infusion (Fig. 4).

**PCP Dose Dependence of Steady-State Tissue-to-Serum Ratios.** The brain-to-serum concentration ratio was found to be significantly lower (\(P < .05\)) at the 2.5 mg/kg/day dose (3.2 ± 0.7) compared with the 10, 18, and 25 mg/kg/day doses (4.7 ± 0.5, 4.7 ± 0.9, and 5.0 ± 0.8, respectively; Fig. 5, top). Although the testis-to-serum concentration ratio also appeared to be lower at the 2.5 mg/kg/day dose.
We found that the distribution of PCP into the brain is extremely rapid after i.v. dosing. Within 30 s after dosing, brain PCP concentrations were already at their highest values, and were 8 times higher than serum concentrations (Fig. 1). This rapid uptake can be described as a substantial clearance of PCP from the blood on its first pass through the brain, and suggests that there is essentially no barrier to PCP distribution into the brain. In support of this hypothesis for barrier-free distribution of PCP into the brain, other studies from this lab using a high-affinity (i.e., 1.8 nM) anti-PCP antibody binding fragment (anti-PCP Fab) show that redistribution (or removal) of PCP out of the brain also occurs extremely rapidly (Valentine and Owens, 1996). However, we realize that the apparent sequestration of PCP in the brain relative to serum concentrations could be due to other factors such as an active uptake process of PCP into the brain or saturable efflux pumps at the blood-brain barrier or metabolism. In previous studies, we have determined the in vivo metabolism of PCP in rat brain and liver (Laurenzana and Owens, 1997). These previous data show that the PCP metabolite formation rate (femtomoles of metabolite per minute per milligram of tissue) in the brain is about 2 to 4% of the formation rate in the liver. Therefore, we do not think that brain metabolism is a significant factor in the partitioning of PCP between the brain and blood.

We also wondered about the impact of the arterial to venous drug concentration gradient on the accuracy of the determination of brain tissue concentrations. It is known that other rapidly acting drugs exhibit a high arterial to venous concentration gradient, especially during the first few minutes after i.v. administration. For instance, Tucker and Boas (1971) observed an arterial to venous concentration ratio of 10:1 for lidocaine immediately after i.v. injection in humans, which decreased quickly over the next 10 min. Because the volume percentage of blood in the brain is so small in the human and the rat (4 and 3%, respectively; Birnbaum et al., 1994) compared with the total volume of brain tissue, temporarily elevated drug concentrations in the arterial blood are unlikely to contribute to the significantly elevated brain-to-serum ratios found in this study. Indeed, we calculated that if concentrations of blood in the brain were actually 10 times
greater than our measured venous concentrations, this would have only resulted in a 10% decrease in our calculated brain concentrations.

The rapid initial distribution of PCP into the brain after i.v. injection of a moderate PCP bolus dose (1 mg/kg) produced very high, but transient, brain PCP concentrations that appeared to be high enough to activate numerous receptor systems and neurochemical pathways not previously thought to be involved in PCP-induced effects (Fig. 6). Certainly, the brain PCP concentrations observed in this study (e.g., 0.1–10 μM) are well above the range of \( K_D \) or \( K_i \) values that have been reported for binding of PCP to sites that are believed to be associated with PCP-induced effects, such as the N-methyl-D-aspartate (NMDA) recognition site (\( K_D = 50–100 \text{ nM} \); Johnson and Jones, 1990) and the dopamine transporter (\( K_i = 400–800 \text{ nM} \); Garey and Heath, 1976; Smith et al., 1986). In addition, the relative abundance of the NMDA receptor and the sigma binding sites (\( K_D = 457 \text{ nM} \); Largent et al., 1986) in the brain is sufficient to bind a significant and measurable amount of PCP. Using \( B_{\text{max}} \) values of 40 to 80 pmol/g wet weight for the NMDA receptor and 15 to 30 pmol/g for the sigma binding site (Largent et al., 1986), we estimate that these two systems could bind a total of approximately 50 ng of PCP. This represents approximately 2% of the PCP that is in the brain at 10 min after an i.v. injection.

An important observation of this study was that concentrations of PCP in the brain did not decrease as rapidly as those in the serum after i.v. injection. This is demonstrated by the rise and fall of the brain-to-serum concentration ratios during the first hour after PCP administration. The brain-to-serum ratio was 8:1 at 30 s and it peaked at approximately 14:1 within the first 20 min. Within 1 h, the brain-to-serum ratio decreased to an equilibrated value of 3:1, which was sustained for the duration of the 8-h sampling period. This difference in rate of decrease in concentrations resulted in a distribution half-life of PCP in the serum that was 30 times shorter than in the brain (Table 1). Thus, although there is a nearly instantaneous distribution of PCP into the brain, distribution out of the brain does not directly parallel the time course of PCP serum concentrations for the first hour after i.v. dosing. This finding implies that serum concentrations do not adequately predict brain concentrations after i.v. dosing.

The time courses of PCP distribution into the brain and the testis after rapid i.v. administration were dramatically different. The partitioning of PCP into the testis after a rapid i.v. dose was greater than, and occurred in a manner distinct from, the brain (Fig. 2). Distribution into the testis appeared to be best described as a diffusion-limited process, unlike distribution into the brain, which appeared to be a blood flow-limited process. Nonetheless, the extensive (i.e., 14:1) partitioning of PCP into the testis after i.v. bolus was dramatic, and most likely due to several factors, including the lipophilicity of PCP and ion trapping of PCP (\( pK_a = 9 \)) in the testis. Furthermore, Wolfe et al. (1989) report that the number of PCP binding sites in the testis is 8 to 9 times higher than the number of NMDA receptor-associated PCP binding sites in the brain. Consequently, high-affinity binding is likely to be a factor in the extensive partitioning of PCP into the testis.

To better understand the potential relationship between the brain and serum PCP concentrations and rate of PCP administration, steady-state tissue-to-serum ratios were determined using a 10-fold range of s.c. infusion doses. These doses range from 2.5 mg/kg/day, which produces no behavioral effects, to an extremely high 25 mg/kg/day dose, which produces profound behavioral effects (Wessinger and Owens, 1991b). At the pharmacologically inactive dose of 2.5 mg/kg/day, steady-state brain-to-serum PCP ratios were 3:1 whereas the brain-to-serum ratios produced at pharmacologically active doses of 10 to 25 mg/kg/day were significantly higher (about 6:1; Fig. 5). The observed brain-to-serum ratio (3:1) with the 2.5 mg/kg/day s.c. dose was identical with the brain-to-serum ratio observed from 1 to 8 h after the 1 mg/kg i.v. dose, which was after the period of pharmacological effects in these and our previous studies (Valentine et al., 1996). These data suggest that only brain-to-serum ratios of greater than 3:1 were associated with behavioral effects in rats after i.v. or s.c. administration.

A similar effect of rate of drug administration on brain and serum concentrations has been observed with nicotine and methamphetamine (Russell and Feyerabend, 1978; Riovrie et al., 1999). Stahlhanske (1970) observes an elevated brain-to-serum nicotine concentration ratio after i.v. dosing that lasts for about 1 h that is not observed after i.p. dosing. Russell and Feyerabend (1978) call this a “bolus-uptake
phenomenon” and suggest that the retention of nicotine in the brain relative to the serum is due to the rapid equilibration between brain and blood nicotine levels, and a subsequent “diifferential retention” arising from binding of nicotine within the brain. We have found that methamphetamine brain and serum concentrations exhibit a similar temporary dynamic disequilibrium after a 1 mg/kg i.v. bolus injection that is not observed after a 1 mg/kg s.c. infusion over 20 h (Riviere et al., 1999). As in the current PCP studies, methamphetamine brain concentrations are highest at the first measured time point (2 min) after i.v. administration, and they decrease more slowly than serum concentrations over the first 1 to 2 h after drug administration. This results in an increase in the brain-to-serum ratio from 7:1 at 2 min to 14:1 at 20 min. After this, the methamphetamine brain-to-serum ratio equilibrates to a constant value of 8:1 (Riviere et al., 1999).

In summary, the results from these studies show that i.v. administration of PCP produces a distinct distribution time course for brain and tests with significant early partitioning of PCP into the brain. This apparent bolus-uptake phenomenon is consistent with reports that show that addiction liability is greatest when drugs are administered by i.v. or smoking routes of administration (Russell and Feyerabend, 1978; Verebey and Godl, 1988; Henningfield and Keenan, 1993). It is unlikely that the slower input resulting from i.p. or i.m. routes of drug administration would produce the pronounced bolus uptake and drug partitioning into the central nervous system as produced with i.v. administration. Finally, these studies could be an important step toward developing an animal model for understanding the pharmacokinetic mechanisms for why some humans prefer more rapid rates of drug input.

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