binary solvent systems are completely defined in this manner. The calculated D_m values of the particular binary solvent system can be plotted (on a large graph) against the percent volume by volume and weight by weight of the polar component of the system. It is possible, then, to select and prepare any mixture of the binary solvent system having a definite dielectric constant.

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Pharmacokinetics of Pentazocine in the Rhesus Monkey

K. A. PITTMANˣ **and G. A. PORTMANN**

Abstract □ The time course of pentazocine concentration was followed in the plasma and cerebrums of individual monkeys by obtaining serial samples of both tissues after intravenous administration of tritiated drug. Plasma concentrations of pentazocine were also followed in a monkey after portal vein infusion. A three-compartment open-system model adequately fits the observed plasma data. The use of the constants derived from that model to predict the time course of pentazocine concentration in the brain results in a good fit with the observed cerebral concentrations. As expected, portal vein infusion caused a reduction in the area below the plasma concentration–time curves and in the percentage of pentazocine excreted in the urine. The relative proportions of known metabolites and their conjugates in urine were determined.

Keyphrases □ Pentazocine—pharmacokinetics, correlation between plasma and brain concentrations, rhesus monkey □ Pharmacokinetics—pentazocine, correlation between plasma and brain concentrations, rhesus monkey □ Plasma concentration, pentazocine—correlated with brain concentration, rhesus monkey □ Brain concentration, pentazocine—correlated with plasma concentration, rhesus monkey

Pentazocine, unlike morphine and a number of its surrogates, is present in brain tissues in much higher concentration than it is in the corresponding plasma after parenteral administration to cats (1), monkeys (2), mice (3), and rats (4). Brain plasma concentration ratios were found to be relatively constant in the rat (4) and rhesus monkey (2) but not as constant in the mouse (3). Pentazocine concentrations in the cerebrum, cerebellum, thalamus, midbrain, pons, and medulla of the rhesus monkey were similar at various times after administration of 0.5 mg/kg im of the drug (2). In addition, only pentazocine, not any of its metabolites, was found in the brain after parenteral administration of tritiated pentazocine or of nonradioactive pentazocine (1–4), implying that the analgesic activity of pentazocine resides in the parent compound and not in its metabolites. In man, peak analgesia after intravenous administration occurred at a time approximately coincident with the apparent end of the distributive phase of the plasma concentration–time curve (5). After intramuscular administration, peak analgesia coincided approximately with the end of the absorption phase (5). Similar results were found in the rat (6) but not in the mouse (3).

The purpose of the reported experiments was to demonstrate that a kinetic model based on the plasma concentration–time curve could be used successfully to predict pentazocine kinetics in another tissue, especially the brain, and, therefore, that any physiological response that could be correlated with plasma pentazocine concentrations could also be correlated with brain pentazocine concentrations.

The rhesus monkey was used because the metabolism of pentazocine has been studied more thoroughly in this species than in others and is known to be similar to that in man. Moreover, its brain is sufficiently large to permit the removal of multiple samples of cerebral tissue.

EXPERIMENTAL

Chemicals—Pentazocine [1,2,3,4,5,6 - hexahydro - *cis* - 6,11-dimethyl-3-(3-methyl-2-butenyl)-2,6-methano-3-benzazocin-8-ol] and pentazocine labeled with tritium in the 4-position were pre-

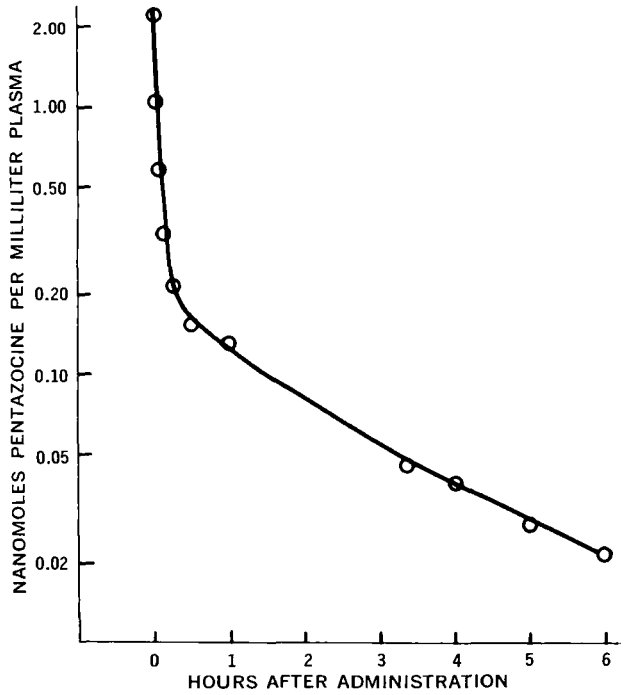


Figure 1—*Plasma levels of pentazocine* versus *time in a 3.75-kg monkey (No. 5635) after 2.04 mg iv (7148 nmoles). The equation fitting the curve is* $2.7e^{-21t} + 0.12e^{-0.82t} + 0.10e^{-0.26t}$. *Key: O, experimental values; and ——, predicted curve.*

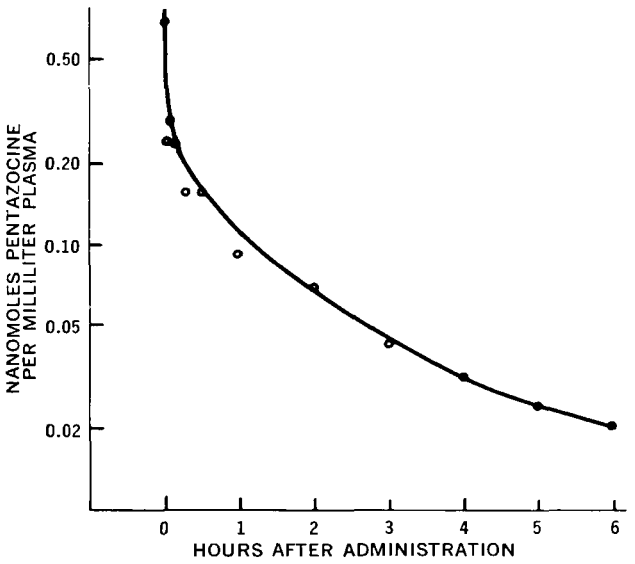


Figure 2—*Plasma levels of pentazocine* versus *time in a 4.78-kg monkey (No. 5269) after 2.41 mg iv (8444 nmoles). The equation fitting the curve is* $0.54e^{-25t} + 0.17e^{-1.1t} + 0.074e^{-0.22t}$. *Key: O, experimental values; and — , predicted curve.*

pared[1]. All other chemicals were analytical reagent grade or better.

Doses—Doses were prepared as 0.1% (w/v) solutions of tritiated pentazocine in lactic acid. Their specific activity was different in each experiment, being approximately 190 Ci/mole for the systemic intravenous doses, administered at about 0.5 mg/kg, and approximately 316 Ci/mole for the portal infusion dose, administered at 1.4 mg/kg.

Animals—Young adult female rhesus monkeys (*Macaca mulatta*), weighing 3.8–4.8 kg, were used. The animals were maintained on the premises for at least 3 months before use and were normal and healthy in all respects.

Design and Execution—One monkey (No. 4851) was restrained in a primate chair, its bladder was catheterized, and an in-dwelling venous catheter was placed in a saphenous vein. The dose was injected rapidly through the saphenous catheter. For the first 6 hr after administration of the dose, sterile Ringer's lactate solution was infused at about 1 ml/min *via* the saphenous catheter. Blood samples were drawn from surface veins on either arm at intervals for 6 days. Urine and feces were collected at intervals for 7 days; the urinary catheter was removed after the first 24 hr.

This monkey was returned to its cage for recovery, and 2.5 months later it was used for the portal vein infusion experiment. By this time, there was no trace of radioactivity in the plasma or excreta. For the portal infusion experiment, the monkey was anesthetized with 3% sodium pentobarbital, its peritoneal cavity was opened, and a cannula was placed in a small vein feeding the portal vein. The end of the cannula was slipped past the junction of the small vein with the portal vein, and the body of the cannula was tied in place in the small vein. The dose (5.94 mg in 3.7 ml) was infused[2] at rates of 10 ml/hr for 15 min and of 3.4 ml/hr for 21 min. Lactated Ringer's solution was used to rinse in the dose, and this infusion was continued for the course of the experiment. Blood was drawn from a saphenous vein cannula, and urine was collected by bladder catheter as before.

In the experiments in which serial brain samples were to be taken, Monkeys 5635 and 5269 first were anesthetized lightly with sodium pentobarbital. Then a urinary catheter was inserted, the animals were tied to a restraining board, a femoral vein was exposed, and in-dwelling venous catheters were placed in the femoral vein and in the saphenous vein of the opposite leg. Ringer's lactate was infused as before through a three-way stopcock. A syringe containing 5% sodium thiopental was attached to the second inlet of the stopcock, and, when required, the minimum amount of this solution necessary to maintain the animal under light anesthesia was injected into the saphenous vein. After insertion of the venous catheters, the scalp was reflected, the right and left lateral aspects of the parietal bone were opened with a 1.27-cm (0.5-in.) trephine, and incisions were made through the dura. Except for the time during which a sample was being obtained, the trephined holes were plugged with gelatin sponge[3] to reduce leakage of cerebral-spinal fluid, and the scalp was pulled over the skull to reduce drying and capillary hemorrhage.

Brain samples were obtained by aspiration with a syringe attached to an 11-gauge stainless steel cannula with a 90° point and an inside bevel. The cannula was inserted through the incision in the dura, deep enough into the cerebrum to obtain an adequate sample but not so deep as to injure the opposite leptomeninges. The average sample weight was 52 mg, with the lowest being 26 and the highest 86. After each puncture, fresh gelatin sponge was fitted into the hole in the skull, the scalp was laid in place, the cannula was washed with water and 70% alcohol and dried, and a fresh syringe was fitted to the cannula. To reduce the effect of trauma caused by one biopsy upon the following biopsies, only four samples were taken from each cerebral hemisphere and these were taken in a radial pattern as follows: anterio-medial, anterio-lateral, posterio-lateral, and posterio-medial. Blood samples were taken from the femoral vein cannula.

At the end of the experiment, the animals were killed by the injection of excess sodium thiopental and the brain was exposed, removed intact, and examined for hemorrhage or edema and for the location of the biopsy sample tracts. The tracts left from biopsy were filled with normal clotting, and some edema had occurred around the incision with only minimal swelling of the cerebrum above the normal limit of the dura.

Analytical Methods—Total radioactivity in blood and in cerebral samples was determined by combustion analysis. Measured volumes of blood were dried on filter paper and wrapped in filter paper. Weighed samples of cerebrum were air dried on weighing paper and wrapped in filter paper. These packages were com-

[1] Dr. N. F. Albertson and Dr. G. D. Diana, Sterling-Winthrop Research Institute.

[2] Holter infusion pump, model RD-174, Extracorporeal Medical Specialties, Inc.

[3] Gelfoam, The Upjohn Co.

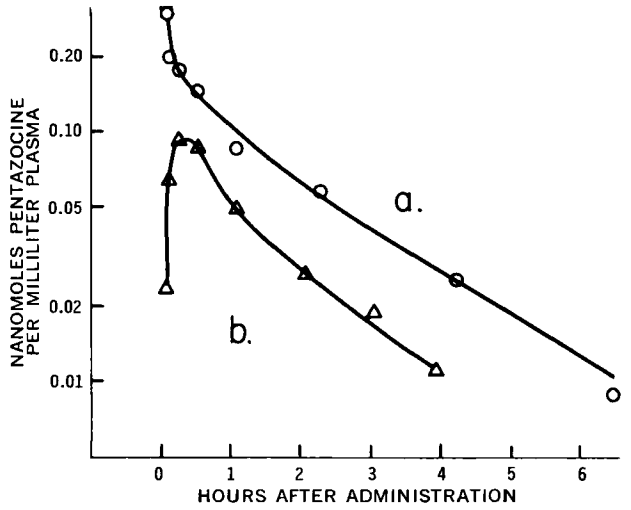


Figure 3—(*a*) *Plasma levels of pentazocine* versus *time in a 3.97-kg monkey (No. 4851) after 2.0 mg iv (7010 nmoles). The equation fitting the curve is* $1.1e^{-23t} + 0.086e^{-1.6t} + 0.13e^{-0.39t}$. *Key:* O, *experimental values; and* ——, *predicted curve.* (*b*) *Plasma levels of pentazocine* versus *time in a 4.23-kg monkey (No. 4851) after a portal infusion of 5.94 mg (20,800 nmoles). Key:* △, *experimental values.*

pressed[4] into hard pellets and combusted[5] for the recovery of tritium as tritiated water. The count rate in the least active sample was about 100 times the background count rate. Total radioactivity in plasma and urine was determined by the direct counting of appropriate samples.

Pentazocine in plasma was determined by adding 0.25 mg pentazocine and 40 mg of an equal mixture of sodium bicarbonate and sodium carbonate to 1 ml of plasma, extracting five times with 5 ml of benzene, reducing the combined benzene extracts to dryness, taking the residue up in a small volume of methanol, and spotting the solution on 5 × 20-cm commercial silica gel plates[6]. The plates were developed in benzene–methanol–isopropylamine (95:5:3 by volume). After development, the band corresponding to pentazocine was scraped, pelleted, and combusted in a manner similar to the brain samples.

Pentazocine and metabolites in urine were determined by adding unlabeled standards to urine samples, desalting the samples by a column[7] method (7), separating pentazocine and metabolites on thin-layer plates in the solvent system already described, and determining the tritium content of the appropriate bands from each plate. The same analysis was also performed on urine samples after enzyme treatment to hydrolyze conjugates (7).

All counts of radioactivity were corrected to disintegrations by a channels-ratio quench correction procedure (8).

Table I—Pharmacokinetic Analysis of the Time Course of Pentazocine Concentrations in the Plasma of Three Rhesus Monkeys Given the Drug Intravenously[a]

Derived Value[b]	Monkey Number (mg/kg)		
	5635 (0.54)	5269 (0.50)	4851 (0.50)
V_C (liters)	2.45	10.8	5.33
W_{FC} (kg)	1.40	1.55	—[d]
K (hr^{-1})	4.43	1.53	3.04
K_{CF} (hr^{-1})	13.3	14.9	14.1
K_{FC} (hr^{-1})	2.18	8.33	4.51
K_{CS} (hr^{-1})	1.88	1.05	2.25
K_{SC} (hr^{-1})	0.479	0.475	1.02
Area: dose (hr kg/ml)[c]	34.6×10^{-5}	29.0×10^{-5}	24.7×10^{-5}

[a] Pentazocine was administered intravenously in aqueous solution, and blood samples taken at various times thereafter for the determination of plasma pentazocine. See text for experimental details. [b] V_C = volume of central compartment, W_{FC} = weight of fast compartment, K = sum of all excretion and metabolic rate constants, K_{CF} = rate constant for movement of pentazocine from central to fast compartment, K_{FC} = rate constant for movement of pentazocine from fast to central compartment, K_{CS} = rate constant for movement of pentazocine from central to slow compartment, and K_{SC} = rate constant for movement of pentazocine from slow to central compartment. [c] The area was determined by integration of the equations describing the plasma concentration–time curves for each monkey. [d] Brain pentazocine levels were not determined.

RESULTS AND DISCUSSION

Concentrations of total radioactivity in blood samples were compared to such concentrations in the corresponding cerebral

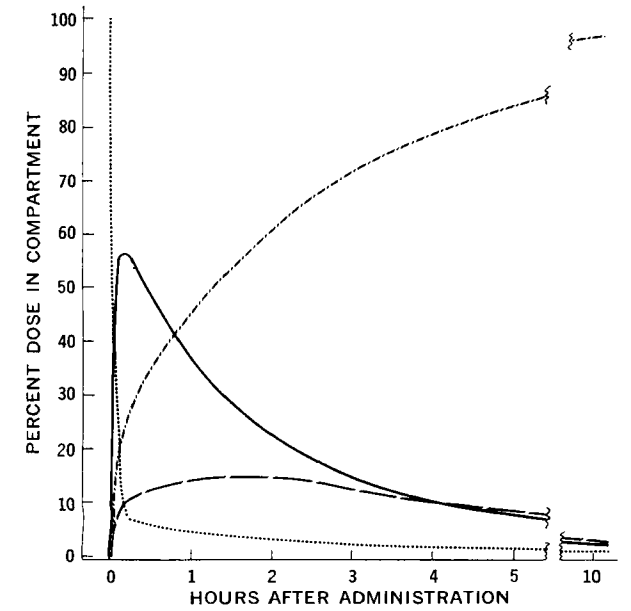


Figure 4—*Calculated percent of a pentazocine dose in various compartments* versus *time in Monkey 5635 after 0.54 mg/kg iv. Key: - - -, central compartment;* ——, *fast compartment; — —, slow compartment; and —·—, metabolized and excreted pentazocine.*

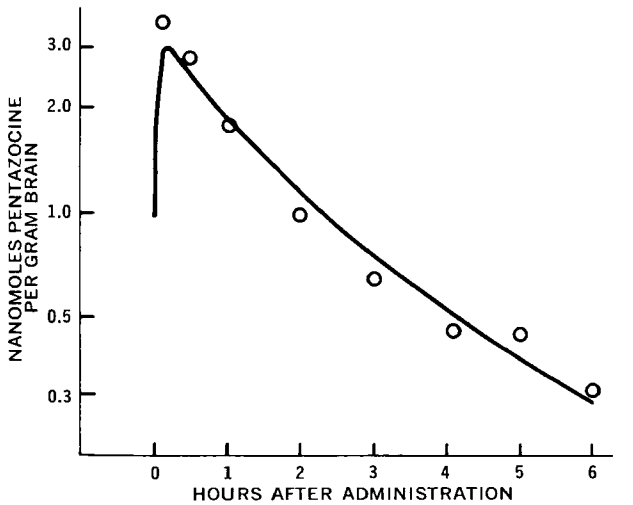
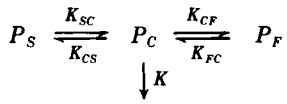


Figure 5—*Pentazocine brain levels* versus *time for Monkey 5635 after 2.04 mg iv (7148 nmoles). The experimental values* (O) *and calculated curve for the fast compartment are shown.*

[4] Stokes tablet machine, model A, F. J. Stokes Machine Co.
[5] Packard Tri-Carb sample oxidizer, model 300, Packard Instrument Co.
[6] Silica gel F-254, E. Merck, Darmstadt, Germany.
[7] XAD-2.



Scheme I

samples. From early to late sampling times, blood values ranged from one-fourth to three-fourths of the brain values. Therefore, the small amount of blood expected to be present in the cerebral samples would not affect the determination of total radioactivity therein significantly. Based on these data and on the fact that only pentazocine and none of its metabolites enter the brain of the rhesus monkey (2) as well as other species (1, 3, 4), the concentration of total radioactivity in the cerebral samples was used as an adequate estimate of pentazocine concentration.

Graphical analysis of semilogarithmic plots of the time course of pentazocine concentration in the plasma of intravenously dosed monkeys (Figs. 1–3) revealed the presence of three first-order components. Therefore, a three-compartment model (Scheme I) was postulated to account for pentazocine kinetics in the rhesus monkey. First-order rate constants (K_{CS}, K_{SC}, K_{CF}, and K_{FC}) control pentazocine (P) distribution in the central (C), fast (F), and slow (S) compartments. The overall elimination rate constant (K) is the sum of the first-order excretion and metabolism rate constants. By using standard analytical procedures (9–11), the plasma data were used to calculate the volume of the central compartment, the rate constants, and the area under the curves (Table I). Elimination half-lives ($0.693/K$) for pentazocine from the monkeys were 0.16 (Monkey 5635), 0.45 (Monkey 5269), and 0.23 (Monkey 4851) hr, while the corresponding half-lives for the slowest plasma exponential were 2.7, 3.2, and 1.8 hr.

One might expect from this information that a large proportion of the dose is distributed to the tissues. The theoretical distribution of pentazocine in Monkey 5635 for 10 hr after an intravenous dose was calculated from the data in Table I and is shown in Fig. 4. The rapid distribution of pentazocine from the central to the fast compartment results in the accumulation of almost 60% of the dose in the fast compartment within 10 min after administration. At this time, only about 10% of the dose remains in the central compartment, the rest being metabolized, excreted, or in the slow compartment. From earlier work (2), it was suspected that the tissues served as an important reservoir for pentazocine after parenteral administration. Both the tissues of the fast and slow compartments serve as important reservoirs, as revealed by the calculations summarized in Fig. 4.

Since the high concentrations of pentazocine found in cerebral samples of two parenterally dosed monkeys and the changes in those concentrations with time (Figs. 5 and 6) both indicate that the brain is likely to be a part of the fast compartment of this model, the plasma data obtained in Monkeys 5635 and 5269 were

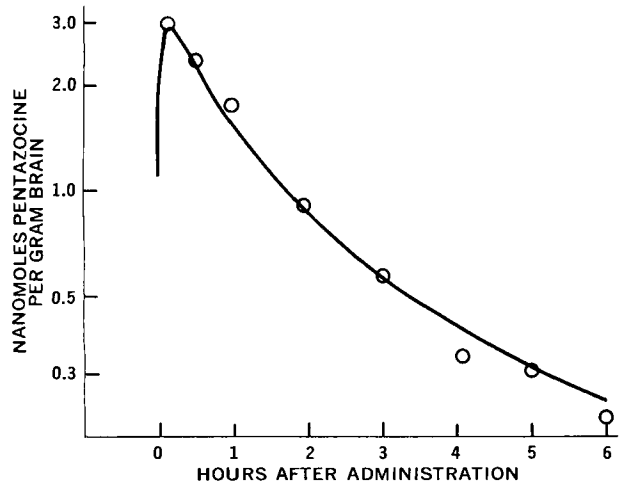
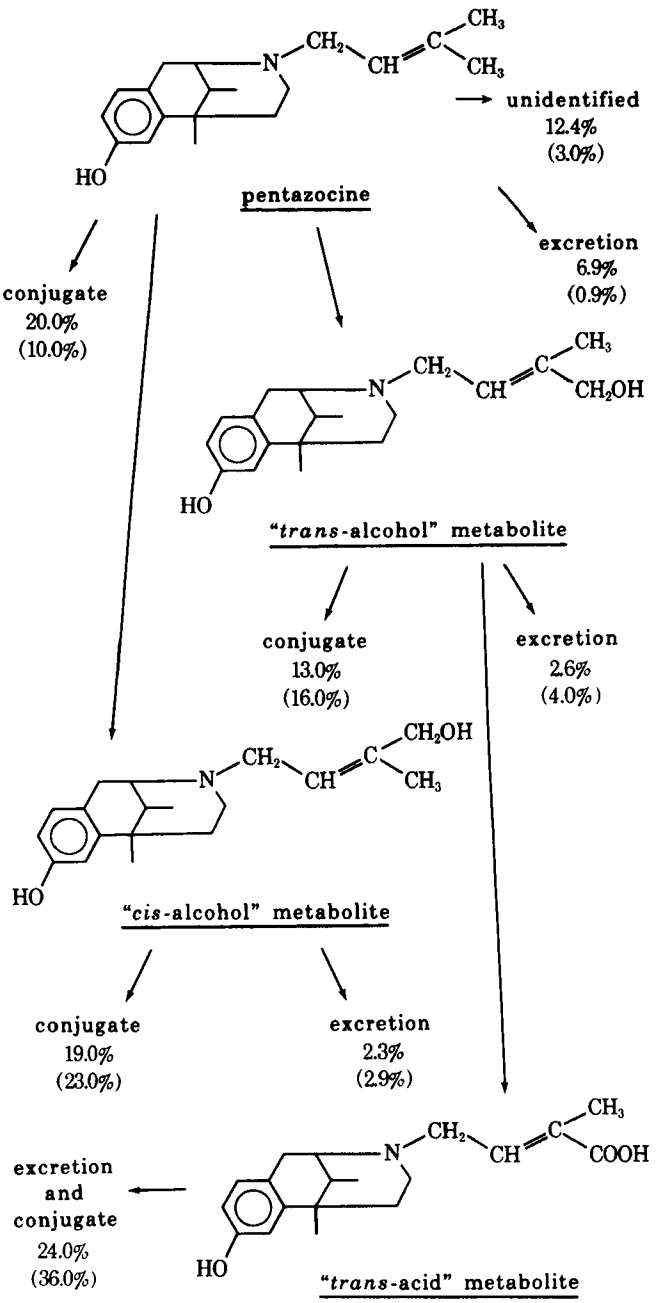


Figure 6—*Pentazocine brain levels* versus *time for Monkey 5269 after 2.41 mg iv (8444 nmoles). The experimental values* (O) *and calculated curve for the fast compartment are shown.*



Scheme II—Pentazocine biotransformation in Monkey 4851 after 0.5 mg/kg iv. Values are expressed as percent of the total amount excreted for 6.9 days. Values in parentheses were obtained for 265 min after a portal infusion of 1.17 mg/kg in the same monkey.

used to predict the time course of pentazocine concentration in the brain. This prediction, which is based on the model, was then compared with the data obtained by repeated sampling of cerebral tissue. The quantity of pentazocine in the fast compartment was calculated according to the model, and a weight term (W_{FC}) was used as a scaling factor for conversion to concentration. Due to differential partitioning and binding of drugs in various tissues within a single pharmacokinetic compartment, any such term is fictitious (12). Therefore, the weight of distribution of the fast compartment (Table I) which was used is as biologically meaningless as the volume of distribution of the central compartment. The results indicate a very close fit between predicted and observed values (Figs. 5 and 6). The fact that such good fits were obtained indicates that the use of a three-compartment model is appropriate for the data and, more importantly, that it is possi-

ble to predict brain concentrations of pentazocine accurately from the plasma data. The information available from studies with other species (1, 3, 4) suggests that the distribution of pentazocine between brain and plasma is similar in all species. Provided that uptake saturation or irreversible effects do not occur, the time course of brain concentrations of pentazocine could be predicted for any species from plasma data and the pharmacokinetic model. No saturation effects were noted in this study with a dose comparable to that used in man.

It is possible that a three-compartment model also is necessary to describe pentazocine pharmacokinetics in man. Data obtained in a clinical study of pentazocine in man[8] indicate that the time course of plasma concentrations of pentazocine after an intravenous dose is similar to that in monkeys. Half-lives for the slowest plasma exponential of pentazocine in man were reported to be about 2 hr in one study (5) and to range between 1.7 and 6 hr in another study (13, 14) after intravenous injection. It seems likely that brain concentrations (and therefore analgesia) of pentazocine in man could be predicted from plasma concentrations and based on a pharmacokinetic analysis.

The so-called "first-pass effect" (15) is quite evident when plasma pentazocine concentrations after injection of the drug into the systemic circulation are compared to concentrations after portal vein infusion (Fig. 3). The relative area under the plasma curve after portal vein infusion is only 14% (3.54×10^{-5} hr kg/ml) of that after intravenous injection (Table I). This effect also is reflected in the relative proportions of pentazocine and its metabolites excreted in the urine (Scheme II). After portal vein infusion, the amount of pentazocine excreted, relative to the dose, is only 13% of that excreted after intravenous injection. The excretion of conjugated pentazocine is also reduced, but the proportions of other metabolites are increased. This dramatic effect of hepatic metabolism upon plasma levels was noted in earlier work (2). Our data[8] and that of others (5, 13, 14) show that the same effect occurs in man.

The metabolism of pentazocine in the monkey as observed in this study agrees closely with that reported earlier (16). The relative proportions of each metabolite plus conjugate excreted are quite similar.

CONCLUSIONS

In the rhesus monkey, brain concentrations of pentazocine are in rapid equilibrium with plasma concentrations of pentazocine. Brain concentrations of pentazocine at any point in time can be predicted on the basis of a three-compartment pharmacokinetic model and known plasma concentrations. The rhesus monkey provides an excellent model for the pharmacokinetic study of drugs with central nervous system activity, because multiple samples of cerebral tissue can be obtained from one animal during the experiment.

[8] K. A. Pittman and G. A. Portmann, unpublished data.

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