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Physiological pharmacokinetic model for pentazocine. I. Tissue distribution and elimination in the rat

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Summary

A physiologically based pharmacokinetic model was developed to describe the tissue distribution and elimination of pentazocine in the anesthetized rat. The model incorporates renal and hepatic (metabolic and biliary) elimination, GI secretion, GI reabsorption and tissue-to-blood partition coefficients. The dependency of hepatic blood flow rate on the arterial blood concentration of pentazocine is also included in the model. Excellent agreement was obtained between the predicted and observed concentrations of pentazocine in tissues and in arterial blood after a 2 mg/kg intravenous dose. Non-linear dose-dependent blood concentration–time profiles after intravenous injection of 0.5–10.0 mg/kg were successfully interpreted with the present model.

Introduction

Pentazocine is a strong analgesic and weak narcotic antagonist, and is useful for clinical application. To characterize the general disposition of this drug, several investigators have adopted conventional compartment analysis for the blood level of pentazocine in animals and humans (Pittman and Portmann, 1974; Vaughan and Beck 1974; Agurell et al., 1974; Ehrnebo et al., 1977; Arakawa et al., 1979). However, in the absence of anatomical reality for each compartment, such compartment analytical results were unable to clarify the time course of pentazocine in particular target organs as an index of the pharmacological effect. There are also

some reports on tissue levels of pentazocine in animals (Ferrari et al., 1968; El-Mazati et al., 1971; Ikeda et al., 1979). However, these reports are limited to qualitative descriptions of the tissue levels of the drug. To overcome the deficiencies of the conventional pharmacokinetic model based on utilization of such tissue level measurements, physiological pharmacokinetic models have recently been developed which employ or incorporate all available data concerning mass transport and the physiology of mammalian systems for the prediction of drug disposition (Bischoff et al., 1968, 1971; Benowitz et al., 1974; Harrison et al., 1977; Tterlikkis et al., 1977; Tsuji et al., 1979). These models permit a precise description of the time course of the drug concentration in any organ or tissue. They are also potentially capable of predicting the disposition kinetics of a drug dependent on changes in anatomical and physiological parameters such as the blood flow and organ volumes.

The present report describes a physiologically based pharmacokinetic model for the distribution and elimination of pentazocine in rats.

Materials and Methods

Materials

Pentazocine (Sankyo, Japan) and levallorphan (Takeda, Japan) were used without further purification. All other reagents were of analytical reagent grade.

Animals

Male albino Wistar rats, 290–320 g, were fasted overnight by giving water freely and used under urethane anesthesia (1.3 g/kg, i.p.).

Protein binding of pentazocine to serum

An acrylic resin plate with 4 compartments, 5 mm in depth and 25 mm in diameter, was used for the dialysis study. Two plates were joined tightly, holding a visking membrane between them. Aliquots (0.8 ml) of rat serum were placed into one compartment and 0.8 ml of pH 7.4 isotonic phosphate buffer containing 0.1–75 μg/ml pentazocine was put into the other compartment. The plates were incubated for 8 h at 37°C. After equilibration, the drug concentrations in both compartments were measured.

Transport of pentazocine to red blood cells

After intravenous injection of pentazocine to rats, blood was withdrawn through the femoral artery at specified time intervals. Part of the blood was centrifuged and divided into plasma and blood cells, and then analyzed for the pentazocine concentration in the plasma and whole blood (0.1–5 μg/ml). The pentazocine transport to red blood cells was also examined in vitro. One minute after mixing pentazocine (1–20 μg/ml) with pooled blood, the mixture was treated in a similar way to that mentioned above.

Injection and sampling

Pentazocine was injected over 2 min via the femoral vein of rats. Blood samples

were withdrawn through a cannula via the femoral artery at specified time intervals after the injection, collected in heparinized tubes and hemolyzed with an equal volume of distilled water. Urine and bile samples were collected at specified time intervals through catheters set in the bile duct and bladder.

The rats were sacrificed at specified times after pentazocine dosing, by injection of air into the femoral vein. The brain, heart, liver, lung, kidney, thigh bone, skin, fat and intestine were excised, rinsed well with saline, blotted, weighed and homogenized with saline (except that Krebs-Ringer solution was used for the liver homogenation to prevent further biotransformation of the pentazocine (El-Mazati and Way, 1971). The pentazocine in the homogenized tissues and blood was extracted with organic solvent at pH 10.2 as described below.

To determine the tissue-to-blood partition coefficient at the steady-state, infusion studies were performed by injection of a loading dose of 5 mg/kg, followed by constant infusion of pentazocine at a rate of 1.6 μg/min. After 6 h, the animals were sacrificed and the pentazocine concentration in various tissues and the arterial blood was determined.

Hepatic venous sampling and determination of the hepatic blood flow rate

A loading dose of 0.05–5 mg/kg of pentazocine was injected, followed by constant infusion of pentazocine at a rate of 0.1–20 μg/min via the femoral vein of anesthetized rats set in the supine position. After 4 h, 0.3 ml of blood was withdrawn via both the femoral artery and the hepatic vein, and the pentazocine concentrations were measured. For estimation of the hepatic blood flow rate, indocyaninegreen (ICG) was infused simultaneously at a rate of about 100 μg/kg/min via the contralateral femoral vein 4 h after the continuous infusion of pentazocine. After 1 h, 0.4 ml samples of blood from both the femoral artery and the hepatic vein were withdrawn at specified time intervals. The ICG concentration in the hepatic venous and arterial plasma and the pentazocine concentration in the arterial blood were measured separately, and the hepatic blood flow rate was calculated according to Yokota et al. (1976).

Drug assay

The pentazocine in the whole blood, plasma, and various tissues was assayed by a GLC method using an electron-capture detector. The detection limit of the method was 5 ng/ml for blood samples and 5 ng/g for tissues. The samples were treated as follows: 1 ml of whole blood or 1 ml of homogenized tissue solution and 0.2–2 μg of levallorphan as an internal standard were added to a 10-ml test tube containing 0.5 ml of carbonate buffer (1 M, pH 10.2). After shaking with 4 ml of ether on a mechanical shaker for 10 min, the two phases were separated by centrifugation and frozen in a dry-ice acetone bath. The ether layer was then poured into a second tube containing 2 ml of 0.1 M H_2SO_4. After shaking for 5 min, the mixture was centrifuged for 5 min, frozen in a dry-ice acetone bath, and the ether layer was discarded. To the remaining aqueous phase, 0.2 ml of 6 N NaOH and 1 ml of ethylacetate were added, and the mixture was shaken on a mechanical shaker for 5 min, centrifuged for 5 min, and frozen in a dry-ice acetone bath. The ethylacetate

phase was poured into a a tapering tube and evaporated to dryness under reduced pressure. The residue was dissolved in 0.2 ml of 5% (v/v) heptafluorobutyric anhydride in ethylacetate and the solution was heated at 60°C for 20 min. Finally, the solution was evaporated to dryness under reduced pressure at 60°C and the residue was dissolved in 50 μl of ethylacetate. Two μl of the solution was injected into a gas-chromatograph.

GLC method

The gas chromatograph (Model GC7A, Shimadzu, Japan) was equipped with an electron-capture detector and a 2.1 m × 3 mm glass column packed with 100% OV-1 on 100–200 mesh Gas Chrom Q. The gas chromatography was carried out under the following conditions: temperature of injection and detector parts, 300°C; column oven temperature, 260°C; nitrogen (carrier gas) flow rate, 60 ml/min.

Results and Discussion

Intravenous bolus injection studies

The time course of pentazocine in the arterial blood after injection of pentazocine (0.5–10.0 mg/kg) via the femoral vein in anesthetized rats over 2 min was fitted to a 3-compartment open model. The studies were repeated using 3 or 4 rats at each dose. Non-linear least-squares regression analysis was carried out using a digital computer (FACOM M 170F, Data Processing Center, Kanazawa University). Fig. 1 gives typical results at an injection dose of pentazocine of 2 mg/kg. The partial pharmacokinetic parameters are listed in Table 1, showing non-linear dependence of the distribution volume and total body clearance with respect to dose.

The cumulative amount of pentazocine in the urine was 3.3 ± 0.5% of the initial

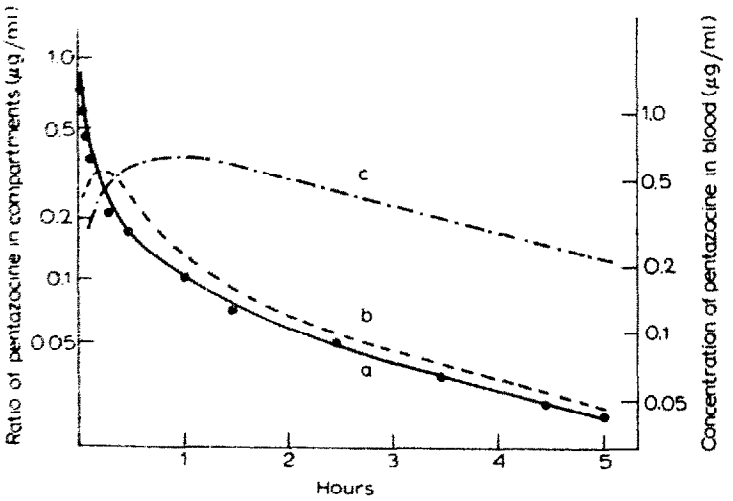


Fig. 1. Time course of arterial concentration of pentazocine and the calculated ratio to initial dose of pentazocine (●) in 3-compartment analysis after a 2 mg/kg injection over 2 min in the rat. Key: a, central compartment; b, shallow compartment; c, deep compartment.

TABLE 1

PHARMACOKINETIC PARAMETERS IN 3-COMPARTMENT ANALYSIS FOR AN INTRAVENOUS DOSE OVER 2 MIN IN THE RAT

	0.5 mg/kg	2 mg/kg	5 mg/kg	10 mg/kg
V_1 (ml)	305 ± 15	370 ± 23	435 ± 28	490 ± 31
K_{el} (min^{-1})	0.032 ± 0.002	0.034 ± 0.003	0.033 ± 0.003	0.034 ± 0.004
Apparent total clearance (ml/min)	9.7 ± 0.9	12.6 ± 1.0	14.4 ± 1.0	16.6 ± 1.5

dose during 24 h after a 2 mg/kg intravenous dose. The cumulative amounts of pentazocine and its glucuronide in the bile during 24 h after injection were below 0.5% and 31.0 ± 4.2%, respectively.

Protein binding of pentazocine to plasma and transport to red blood cells

The percentage of plasma protein binding of pentazocine was 46.0 ± 2.5%, and was independent of the initial drug concentration below 20 μg/ml (n = 7).

The blood:plasma concentration ratio of pentazocine was 1.55 ± 0.08 and almost the same both in vitro (n = 8) and in vivo (n = 6), the value being independent of the pentazocine concentration below 20 μg/ml. Equilibration of pentazocine between plasma and red blood cells was achieved within 1 min.

Infusion studies

To clarify the non-linear dependence between dose and total body clearance of pentazocine, infusion studies were performed. Pentazocine (0.5–20 μg/min) was

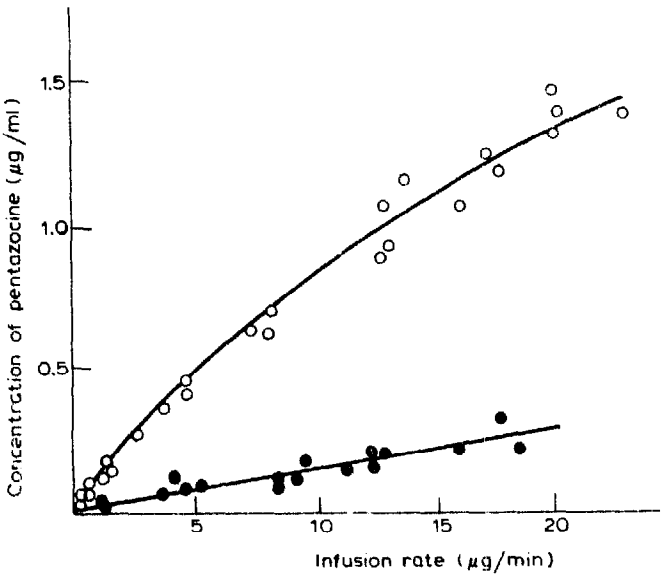


Fig. 2. Concentration of pentazocine in the blood in the steady-state after intravenous infusion of pentazocine to rats. Key: ○, arterial blood; ●, hepatic venous blood.

TABLE 2

ESTIMATION OF HEPATIC CLEARANCE

I_0 (μg/min)	$(C_a)_{ss}$ (μg/ml)	CL^T_{app} (ml/min)	Q_{LV} (ml/min)	CL_H (ml/min)
0.0	0.0		8.5 ± 0.6	
2.6	0.27	9.63	11.3	48.9
3.1	0.3	10.33	12.1	53.9
3.3	0.33	10.0	11.0	72.4
4.6	0.425	10.82	12.9	53.0
7.4	0.63	11.75	14.5	51.1
8.0	0.7	11.43	13.4	60.8
9.9	0.85	11.65	15.4	41.0
10.8	0.88	12.27	15.5	49.8
12.4	0.98	12.65	15.4	58.8
17.4	1.22	14.26	17.0	73.7
17.8	1.27	14.02	17.1	65.6
18.2	1.3	14.0	17.6	58.9
20.8	1.43	14.55	19.0	54.6
				57.1 ± 8.7

infused after a bolus injection (0.5–5 mg/kg) over 2 min, and the concentrations of pentazocine in both the arterial and hepatic venous blood were measured after establishment of steady-state conditions. As shown in Fig. 2, the arterial pentazocine concentration was depressed with increasing infusion rate, while the concentration in the hepatic veins was proportional to the infusion rate of pentazocine.

Relation between hepatic blood flow rate and concentration of pentazocine in the arterial blood

There was no significant change in protein binding or blood:plasma concentration ratio of pentazocine with increasing blood levels as mentioned above. The hepatic extraction ratio of pentazocine was estimated to be 0.75–0.85 from the results in Fig. 2. It is expected that the change in apparent body clearance dependent on the blood level of pentazocine is due to variation of the hepatic blood flow (Wilkinson and Shand, 1975; Nies et al., 1976; George, 1979). Pentazocine was then infused at various rates to ascertain the relationship between hepatic blood flow rate and arterial blood concentration of pentazocine. The results are summarized in Table 2. CL^T_{app} and CL_H were calculated from Eqn. 1 and Eqn. 2, respectively (Awazu et al., 1977), and are listed in Table 2.

$$CL^T_{app} = \frac{I_0}{(C_a)_{ss}} \tag{1}$$

$$CL_H = \frac{Q_{LV}\left(CL^T_{app} - CL^{KD}_{app}\right)}{Q_{LV} - \left(CL^T_{app} - CL^{KD}_{app}\right)} \tag{2}$$

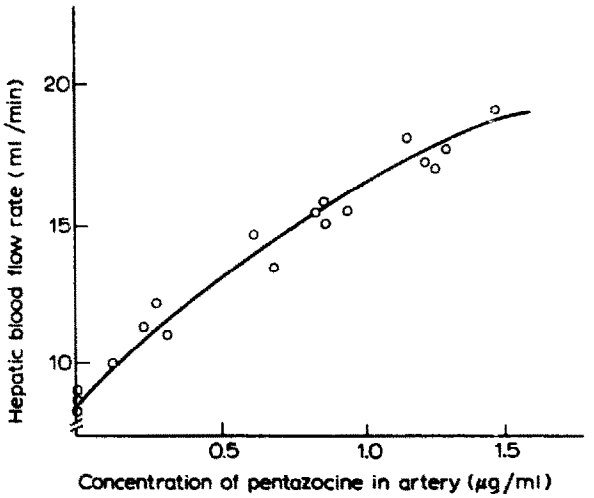


Fig. 3. Relationship between hepatic blood flow measured by the ICG method and arterial concentration of pentazocine in the steady-state after intravenous infusion to rats.

where I_0 is the infusion rate of pentazocine, $(C_a)_{ss}$ is the concentration of pentazocine in the arterial blood at the steady-state, Q_{LV} is the hepatic blood flow rate estimated by the ICG method, CL_H is the hepatic clearance, CL^T_{app} is the apparent total clearance, and CL^{KD}_{app} is the apparent renal clearance (0.45 ml/min) estimated from dividing the urinary secretion rate by the arterial blood concentration of pentazocine at the steady-state.

The relationship between hepatic blood flow and concentration of pentazocine in the arterial blood is illustrated in Fig. 3. In order to describe the hepatic blood flow as a function of the steady-state arterial blood concentration of pentazocine, the following regression equation was derived.

$$Q_{LV} = \frac{27.0(C_a)_{ss}}{2.5 + (C_a)_{ss}} + 8.5 \tag{3}$$

Tissue-to-blood partition coefficient

For determination of the tissue-to-blood partition coefficient of pentazocine in rats, infusion studies were performed at a constant rate of 1.5 μg/min with a loading dose of 0.5 mg/kg using 5 animals. The tissue-to-blood partition coefficients of various tissues except liver were calculated according to the steady-state method of Chen et al. (1979) and that K_{LV} for liver was estimated by Eqn. 4.

$$K_{LV} = K^{app}_{LV} \cdot \frac{Q_{LV} + CL_H}{Q_{LV}} \tag{4}$$

where K^{app}_{LV} is apparent tissue-to-blood partition coefficient, which was determined to be 0.3 ± 0.12. These values are listed in Table 3.

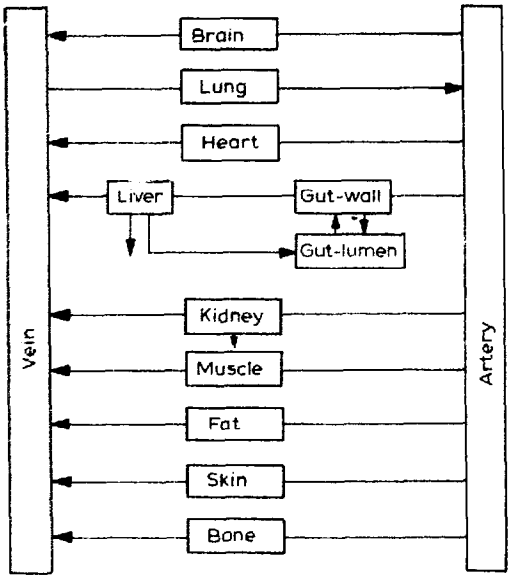
TABLE 3

TISSUE VOLUME, TISSUE-TO-PARTITION COEFFICIENT AND BLOOD FLOW RATE USED IN THE PHARMACOKINETIC MODEL FOR THE RAT

Tissue	Volume	Tissue-to-blood partition coeff.	Blood flow rate (ml/min)
Venous blood	16.0		~ 48.9
Arterial blood	8.0		~ 48.9
Lung	1.3	17.5 ± 5.1	~ 48.9
Brain	1.7	2.8 ± 0.8	~ 1.4
Heart	1.2	3.5 ± 0.6	~ 5.4
Liver	13.0	$0.3 \times (Q_{LV} + 57.1)/Q_{LV}$	$27.0 \times C_a/(2.5 + C_a) + 8.5$
Kidney	3.3	13.0 ± 1.7	14.6
Gut wall	21.3	3.0 ± 0.7	$Q_{LV} \times 0.7$
Gut contents	15.4	–	–
Muscle	150.0	3.8 ± 1.1	8.7
Fat	10.0	1.6 ± 0.4	2.3
Skin	55.3	3.0 ± 1.1	5.8
Bone	30.5	3.5 ± 1.0	1.6

Calculations based on the physiological pharmacokinetic model

Scheme I shows the physiological pharmacokinetic model utilized here for calculation. This model was built up on the basis of the following assumptions: (1) each



Scheme I.

tissue acts as a well-stirred compartment; (2) pentazocine distribution is limited by the blood flow rate; (3) the tissue-to-blood concentration ratio of pentazocine is independent of the drug concentration; and (4) the arterial concentration of pentazocine after bolus injection is assumed to produce the same variation in hepatic blood flow as occurs in the steady-state.

A typical mass balance equation for the venous blood is given by

$$V_{VB}\frac{dC_{VB}}{dt} = DI(t) + Q_{BR}\frac{C_{BR}}{K_{BR}} + Q_{HT}\frac{C_{HT}}{K_{HT}} + Q_{LV}\frac{C_{LV}}{K_{LV}} + Q_{KD}\frac{C_{KD}}{K_{KD}} + Q_{MS}\frac{C_{MS}}{K_{MS}}$$

$$+ Q_{FT}\frac{C_{FT}}{K_{FT}} + Q_{SK}\frac{C_{SK}}{K_{SK}} + Q_{BN}\frac{C_{BN}}{K_{BN}} - Q_{VB}C_{VB} \quad (5)$$

where VB, BR, HT, LV, KD, MS, FT, SK and BN indicate venous blood, brain, heart, liver, kidney, skeletal muscle, fat, skin and bone, respectively. V_i is the actual tissue volume, C_i the total pentazocine concentration bound and unbound to any protein, Q_i the blood flow rate to tissue, K_i the tissue-to-blood partition coefficient, and DI(t) the infusion rate of the total pentazocine dose (μg/min).

The mass balance equation for the liver is given by:

$$V_{LV}\frac{dC_{LV}}{dt} = (Q_{LV} - Q_{GW})C_{AB} + Q_{GW}\cdot\frac{C_{GW}}{K_{GW}} - Q_{LV}\cdot\frac{C_{LV}}{K_{LV}} - (CL_M + CL_B)\frac{C_{LV}}{K_{LV}} \quad (6)$$

where AB and GW indicate arterial blood and gut-wall, respectively, CL_B and CL_M are the clearances of the biliary secretion and metabolism, respectively, which were estimated by dividing the total hepatic clearance (CL_H = 57.1 ml/min) in the ratio of 1 : 2 (see experimental section). The hepatic blood flow was assumed to change with the arterial concentration of pentazocine. The relation between Q_{LV} and C_{AB} was assumed to obey Eqn. 3 for bolus injection as in the steady-state condition.

The mass balance equation for the gut contents is given by:

$$V_{GC}\cdot\frac{dC_{GC}}{dt} = CL_B\cdot\frac{C_{LV}}{K_{LV}} + k_{WC}V_{GW}C_{GW} - k_{CW}V_{GC}C_{GC} - CL_FC_{GC} \quad (7)$$

where GC indicates gut contents. k_{CW} and k_{WC} are the first-order rate constants for gut absorption and secretion, respectively. CL_F is the fecal clearance but was

TABLE 4

CLEARANCE AND RATE CONSTANTS FOR PENTAZOCINE DISTRIBUTION AND ELIMINATION IN THE RAT

Parameter	Estimated value
Metabolic clearance (CL_M)	38.1 ml/min
Biliary clearance (CL_B)	19.0 ml/min
Renal clearance (CL_{KD})	0.46 ml/min
Absorption rate constant (k_{CW})	0.05 min^{-1}
Secretion rate constant (k_{WC})	0.05 min^{-1}

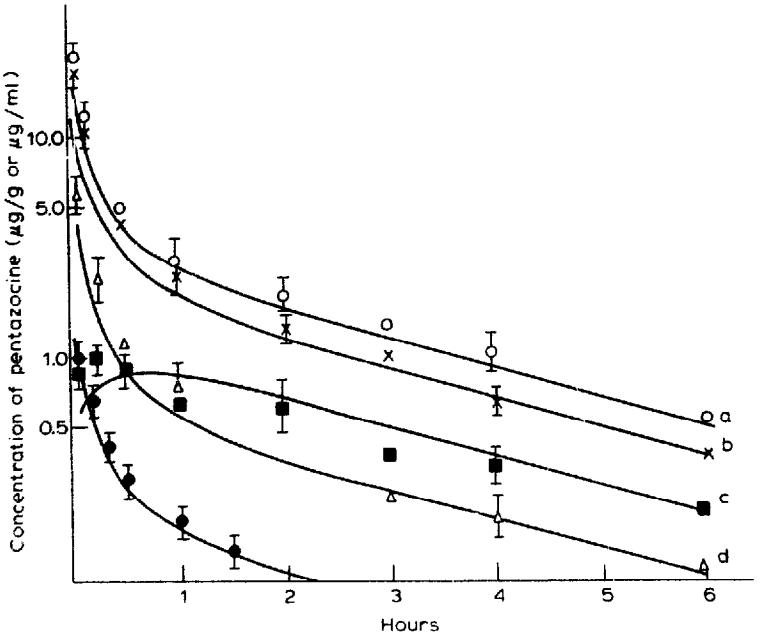


Fig. 4. Predicted and observed concentration of pentazocine in tissue and in arterial blood after a 2 mg/kg intravenous injection over 2 min. Key: a (○), lung; b (×), kidney; c (■), muscle; d (△), heart; e (●), artery.

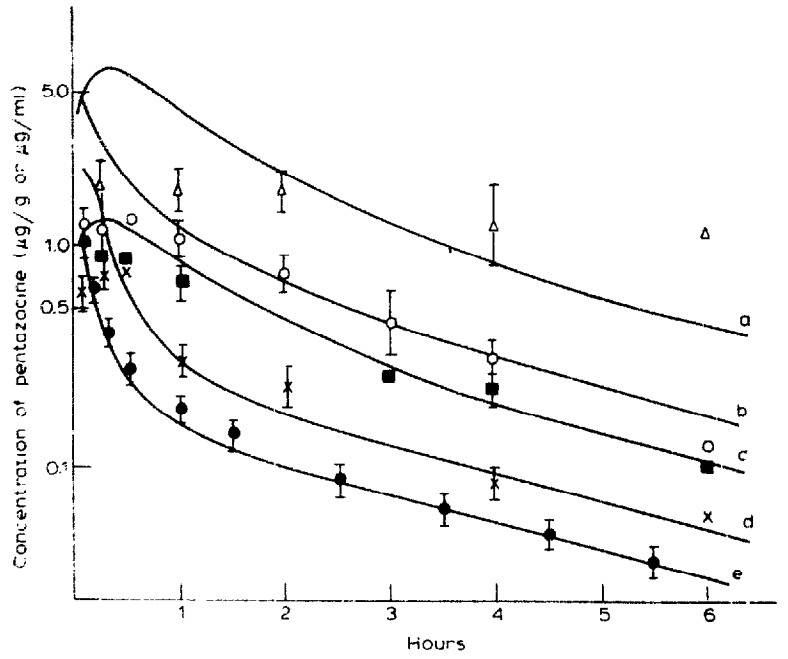


Fig. 5. Predicted and observed concentration of pentazocine in tissues and arterial blood after a 2 mg/kg intravenous injection over 2 min. Key: a (△), gut contents; b, (○), gut wall; c (■), skin; d (×), fat; e (●), artery.

neglected in this study, since the residue of the total pentazocine conjugated and uncongjugated at 24 h after dosing was below 2% of the dose (Ikeda et al., 1979; Fukawa et al., 1979). The first-order absorption rate constant, k_{CW}, was estimated on the basis of the absorption half-life of pentazocine in the rat being about 15 min (Ikeda et al., 1979). The rate constant, k_{WC}, was estimated to be 0.05 min^{-1}, since the steady-state distribution of pentazocine between the gut wall and contents in the bile-duct rats indicated a ratio of rate constant for gut secretion to gut absorption of about 1.

Mass balance equations can be similarly given for the remaining compartments, but the gastrointestinal absorption, renal clearance and hepatic clearance were assumed to be linear. The equations including the assumption were deduced from the enterohepatic recirculation mechanism (Harrison and Gibaldi, 1977; Fukawa et al., 1979) in which glucuronide pentazocine was completely and immediately hydrolyzed. The flow rate and tissue volume were evaluated from reported values for rats (Jansky and Hart, 1968; Bischoff et al., 1971; Dedrick et al., 1973), but the blood flow rates of the internal organs were changed in proportion to Q_{LV} except for the kidney (Yamashiro, 1978). These values are listed in Table 3. The clearance parameters and rate constants used in the simulation are listed in Table 4.

Thirteen differential equations were solved by the Runge-Kutta method using a digital computer. The model-predicted and observed pentazocine concentrations for the blood and various tissues after intravenous dose of 2 mg/kg over 2 min are shown in Figs. 4–6. The predicted and observed concentrations in the arterial blood after an intravenous dose of 0.5–10 mg/kg are shown in Fig. 7. All of the

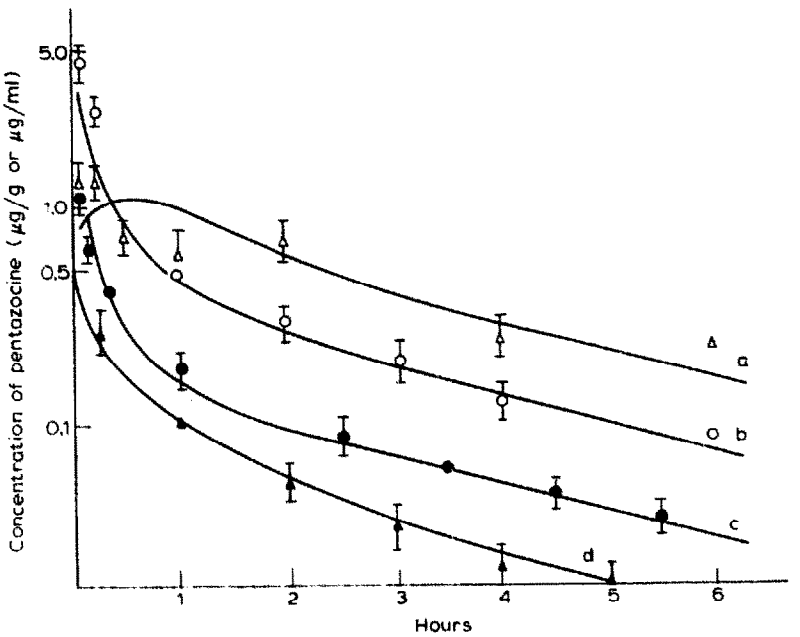


Fig. 6. Predicted and observed concentration of pentazocine in tissues and arterial blood after a 2 mg/kg intravenous injection over 2 min. Key: a (△), bone; b (○), brain; c (●), artery; d (▲), liver.

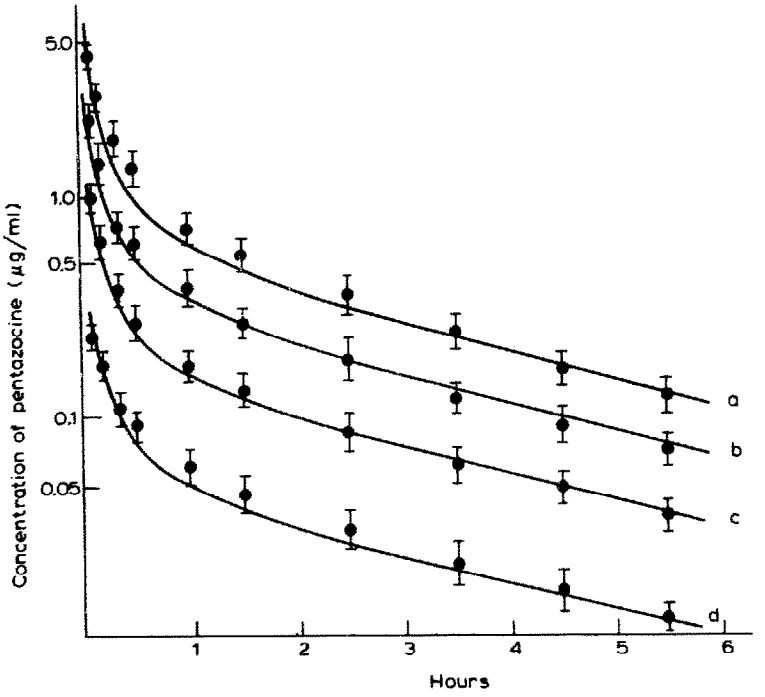


Fig. 7. Predicted and observed concentrations of pentazocine in arterial blood after a 0.5–10 mg/kg intravenous injection over 2 min. Key: a, 10 mg/kg; b, 5 mg/kg; c, 2 mg/kg; d, 0.5 mg/kg.

predictions agreed well with the corresponding observed values. The results indicate that this assumption of a perfusion-limited model for pentazocine by using the partition coefficients in the tissues determined at one dose level could reasonably predict the tissues concentration of pentazocine at other doses. Pentazocine was concentrated more in all tissues (except the liver) than in the blood, suggesting a considerable distribution of pentazocine into the tissues.

Pittman and Portmann (1974) noted that the time course of pentazocine in the brain of the rhesus monkey showed a good fit with the time course of the drug in the shallow compartment obtained by analyzing the plasma concentration of pentazocine in an open 3-compartment model. However, in the present studies on rats, the pentazocine in the shallow compartment reached a maximal level within 10–15 min but all the experimental data obtained in 6 rats indicated that the brain pentazocine concentration reached a maximal level within 3–6 min after intravenous injection over 2 min. We consider that in the rat, the shallow compartment may correspond to the bone and skin tissue compartment, and the brain tissue compartment may be involved in the central compartment.

In this experiment, we used urethane-anesthetized rats. Recently, Pipkin and Stella (1982) showed that thiamine pharmacokinetics were affected by urethane anesthesia when compared to ether anesthesia or unanesthetized animals. The results of pentazocine pharmacokinetics may be limited to urethane anesthetized rats.

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