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Physiological pharmacokinetic model for distribution and elimination of pentazocine. II. Study in rabbits and scale-up to man

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Summary

A physiologically based pharmacokinetic model was applied to describe the distribution and elimination of pentazocine in rabbits. For the elimination of pentazocine, the model consisted of renal, hepatic (metabolic and biliary), and GI secretion and GI re-absorption. The tissue-to-blood partition coefficients of pentazocine in the rabbit were almost the same with those in the rat. No significant variation in hepatic blood flow rate dependent on the arterial blood concentration of pentazocine was observed in the rabbit, the results being very different from those in the rat. The time course of blood concentration after intravenous injection was proportional to dose in the range of 0.5–10 mg/kg. Excellent agreements were obtained between the predicted and observed concentrations of pentazocine after intravenous administration in the rabbit. Application of the rabbit model to prediction in man by considering the differences in organ volume, organ blood flow and renal pentazocine clearance was successful, and the model was adopted to decide the therapeutic dose of pentazocine during surgery of patients.

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Introduction

Conventional compartment models based on curves of the plasma concentration time course to describe the pharmacokinetics of pentazocine have been adopted in animals and man (Pittman et al., 1974; Vaughan et al., 1974; Agurell et al., 1974; Ehrnebo et al., 1977; Arakawa et al., 1977). In these instances, however, each compartment had no anatomical or physiological reality. Moreover, such compartment analysis was unable to clarify the time course of pentazocine concentration in a particular target organ like the brain as an index of the pharmacological effect. To overcome the defects of such compartment models, physiologically based pharmacokinetic models have recently been used for the drug disposition based on organ flows and volumes (Bischoff et al., 1968, 1971; Benowitz et al., 1974; Harrison et al., 1977; Tterlikkis et al., 1977; Tsuji et al., 1979).

A physiological model (Scheme 1) was previously developed by us to describe the pentazocine pharmacokinetics in the rat (Ichimura et al., 1983). This model was employed to describe the time course of blood and tissue concentrations of pentazocine in urethane-anesthetized rats. Although the time course of the blood pentazocine concentration obeyed a non-linear dependence on dose, the model also successfully predicted the time course of the blood concentration limited by the hepatic blood flow rate.

Based on previous studies in the rat, the same physiologically based pharmacokinetic model was applied in the present study to describe the distribution and elimination of pentazocine in the rabbit. This report also gives scale-up results of the animal model to man and its clinical application to patients who received pentazocine for general anesthesia.

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 and patients

White male rabbits, 2.8–3.5 kg, and beagles, 8.5–9.0 kg, were fasted overnight but given water freely. Catheters were aseptically inserted under light anesthesia with ether into the bladder, bile duct, femoral artery and hepatic vein of rabbits, respectively. Eight healthy male patients, 41–67 kg, who were admitted for microscopic laryngeal surgery were allocated for human study.

Injection and sampling

Pentazocine was infused over 2 min by use of infusion pump via the femoral vein of rabbits. Blood samples were withdrawn through a cannula via the femoral artery at specified time intervals after the infusion, 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 into the bile duct and bladder. Pentazocine was infused over 1 min via the femoral vein of beagles and blood samples were withdrawn through a cannula via the contralateral femoral vein at specified time intervals after the infusion. Urine samples were collected at specified time intervals through a catheter inserted into the bladder of the beagles. In 8 surgical patients, pentazocine (1.0 mg/kg) was slowly injected over 1 min via the cubital vein and blood samples were collected through a cannula via the femoral vein at specified time intervals. In 3 of these patients, pentazocine (0.5 mg/kg) was slowly injected 60 min after the initial injection over 1 min as an additional dose.

The rabbits were sacrificed at specified times after the infusion of pentazocine, 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, sliced, homogenized and extracted with saline (except the liver for which Krebs-Ringer solution was used in the homogenation to prevent further biotransformation of pentazocine because of presence of Ca^{2+} (El-Mazati et al., 1971)). The pentazocine in the homogenized tissues was extracted with ether at pH 10.2 in the same manner as described previously in rats (Ichimura et al., 1983).

To determine the tissue-to-blood partition coefficient in the steady-state, infusion studies were performed at a constant rate of 5 μg/kg/min with a loading dose of 1 mg/kg using 5 unanesthetized rabbits. After 6 h, the rabbits were sacrificed and the pentazocine concentration in various tissues and the arterial blood was determined. A part of the blood was centrifuged to obtain plasma. Another part was hemolyzed with an equivalent volume of distilled water. The two samples thus obtained were analyzed for the pentazocine concentration both in the plasma and whole blood.

Hepatic venous sampling and determination of the hepatic blood flow rate

A loading dose of 0.5–5 mg/kg of pentazocine was injected, followed by constant infusion of pentazocine at a rate of 2–35 μg/kg/min via the femoral vein of anesthetized or unanesthetized rabbits set in the supine position. After 4 h, 0.5 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, indocyanine green (ICG) was infused simultaneously at a rate of about 50 μg/kg/min via the contralateral femoral vein under the continuous infusion of pentazocine. After 1.5 h, 0.5 ml samples of blood from both the femoral artery and the hepatic vein were withdrawn at specified time intervals. The ICG concentrations in the arterial and hepatic venous plasma were determined as described by Stoeckel et al. (1980). There was no influence on the assay of ICG in the presence of pentazocine. The pentazocine concentration in the arterial blood was measured as described below.

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 according to the previously described procedures (Ichimura et al., 1983). The

conjugated pentazocine was hydrolyzed with β-glucuronidase (Ikeda et al., 1979) and was then determined by the same method as the non-conjugated pentazocine.

GLC method

The gas chromatography (Model GC7A, Shimadzu, Japan) was equipped with an electron-capture detector and a 2.1 m × 3 mm glass column packed with 10% 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 temperature, 260°C; and nitrogen (carrier gas) flow rate, 60 ml/min.

Results and Discussion

Relation between dose and the total body clearance and hepatic clearance

To clarify the relation between dose and total body clearance, infusion studies were performed in anesthetized and unanesthetized rabbits, because a non-linear dependence between dose and total body clearance had been confirmed previously in rats (Ichimura et al., 1983). Pentazocine (2–35 μg/kg/min) was infused after a bolus injection (0.2–5 mg/kg) over 2 min, and the concentrations of pentazocine in both the arterial, $(C_a)_{ss}$, and the hepatic venous blood, $(C_{HV})_{ss}$, were measured in the steady-state condition. The relationship between infusion rate, I, and concentration of pentazocine in the arterial blood in the steady-state is illustrated in Fig. 1. Clearly, the arterial concentration of pentazocine increased in proportion to the

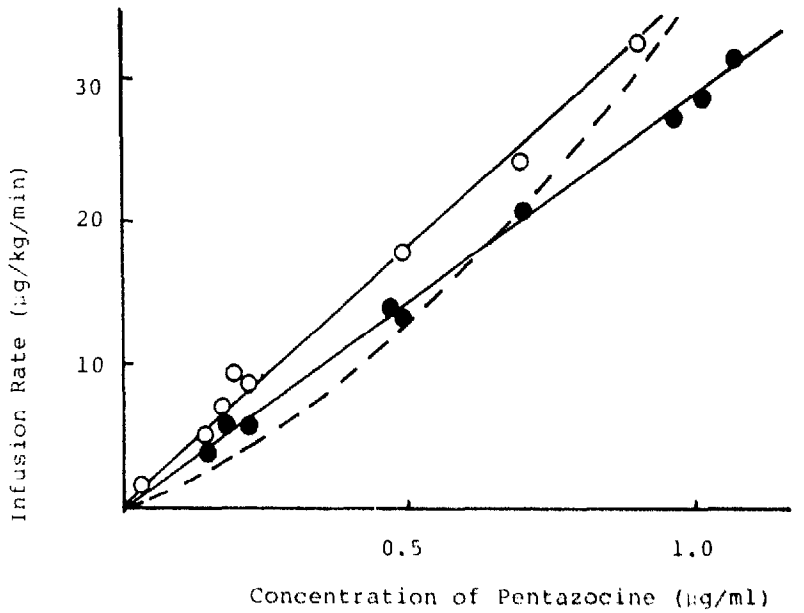


Fig. 1. Concentration of pentazocine in the arterial blood in the steady-state after intravenous infusion of pentazocine to rabbits. Key: ○, unanesthetized rabbits; ●, anesthetized rabbits; - - - - -, anesthetized rats (Ichimura et al., 1982).

TABLE 1

RELATION BETWEEN HEPATIC BLOOD FLOW RATE AND ARTERIAL BLOOD CONCENTRATION OF PENTAZOCINE IN UNANESTHETIZED AND ANESTHETIZED RABBITS IN THE STEADY-STATE CONDITION

Unanesthetized		Anesthetized	
$(C_a)_{ss}$ (μg/ml)	Q_{LV} (ml/min)	$(C_a)_{ss}$ (μg/ml)	Q_{LV} (ml/min)
0.0	165	0.0	132
0.1	169	0.15	128
0.48	179	0.7	138
0.85	170	0.98	122

infusion rate in both anesthetized and unanesthetized rabbits, contrary to the results in the rat (Ichimura et al., 1983).

The percentage of plasma protein binding of pentazocine determined by use of the same method as described in the previous paper (Ichimura et al., 1983) was $60 \pm 2\%$, and was independent of the drug concentration below 20 μg/ml ($n = 15$).

The estimated blood/plasma concentration ratio of pentazocine was 1.55 ± 0.06 and was almost the same both in vitro determined by the similar way described previously (Ichimura et al., 1983) ($n = 8$) and in vivo ($n = 6$), and the value being independent of pentazocine concentration below 20 μg/ml in the whole blood.

Pentazocine was infused at various rates to ascertain the relationship between hepatic blood flow rate and arterial blood concentration of pentazocine in the steady-state. The results are summarized in Table 1. There was no change in the hepatic blood flow under the present experimental conditions, either in the anesthetized or unanesthetized rabbit.

The values of CL^T_{app}, CL_H, CL_{KD} and E in unanesthetized rabbits were calculated from Eqns. 1, 2 and 3, respectively, and also are given in Table 2.

TABLE 2

ESTIMATION OF TOTAL BODY CLEARANCE AND HEPATIC CLEARANCE OF PENTAZOCINE IN UNANESTHETIZED RABBITS

I_0 (μg/ml)	$(C_a)_{ss}$ (μg/ml)	$(C_{HV})_{ss}$ (μg/ml)	E	CL^T_{app} (ml/min)	CL_H (ml/min)
19.5	0.15	0.04	0.73	130.0	368.2
22.5	0.18	0.052	0.71	125.0	322.3
31.0	0.24	0.072	0.70	129.2	360.3
62.5	0.49	0.16	0.67	127.6	345.2
84.0	0.65	0.18	0.72	129.2	360.3
154.0	1.21	0.36	0.70	127.2	342.4

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

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

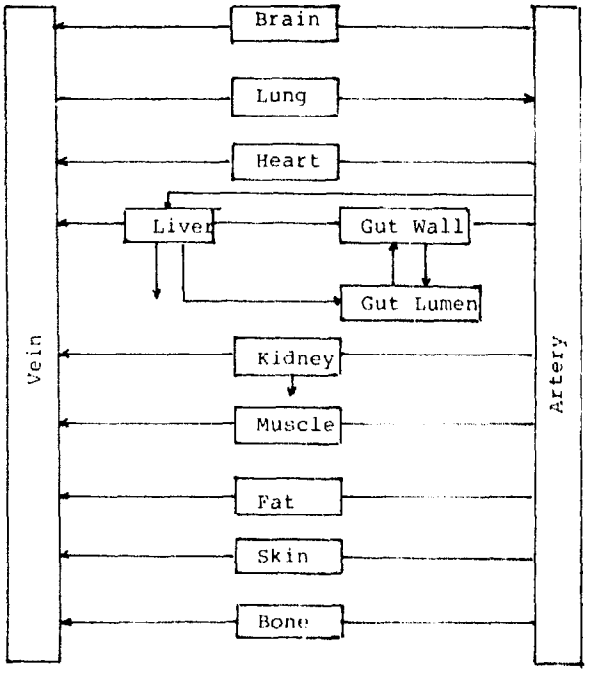
$$E = \frac{(C_a)_{ss} - (C_{HV})_{ss}}{(C_a)_{ss}} \quad (3)$$

$$CL_{KD} = \frac{Q_{KD} \times CL^{KD}_{app}}{Q_{KD} - CL^{KD}_{app}} \quad (4)$$

where CL^{T}_{app} is the apparent total body clearance, CL_H the intrinsic hepatic clearance, Q_{LV} the hepatic blood flow rate, CL^{KD}_{app} the apparent renal clearance (4.2 ml/kg/min) estimated by dividing the urinary excretion rate by the arterial blood concentration of pentazocine in the steady-state, E the extraction ratio, CL_{KD} the intrinsic renal clearance and Q_{KD} the renal blood flow rate.

Tissue-to-blood partition coefficient

The tissue-to-blood partition coefficient in the steady-state was calculated (Chen and Grass, 1979) and the values are listed in Table 3 together with those determined



Scheme 1

TABLE 3

TISSUE-TO-BLOOD PARTITION COEFFICIENTS, TISSUE VOLUMES AND BLOOD FLOW RATE USED IN THE PHYSIOLOGICAL PHARMACOKINETIC MODEL OF PENTAZOCINE FOR ANIMALS AND MAN

Tissue	Tissue-to-blood partition coeff.	Rabbit (3 kg)		Beagle (8.5 kg)		Man (50 kg)	
		Vol. [a] (ml)	Blood Fl. [b] (ml/min)	Vol. [c] (ml)	Blood Fl. [c] (ml/min)	Vol. [c] (ml)	Blood Fl. [c] (ml/min)
Venous blood		158.4	495.5	284.0	958.2	2570.0	4165.0
Arterial blood		79.2	495.5	141.0	958.2	1290.0	4165.0
Brain	3.3 ± 0.4	7.9	5.4	50.4 [j]	145.6 [j]	1070.0 [m]	536.0
Lung	20.7 ± 2.5	21.8	495.5	85.0 [k]	958.2	430.0 [m]	4165.0
Heart	4.1 ± 0.3	7.7	19.6	42.5	42.5	214.0	179.0
Liver	2.1 ± 0.7	128.4	170.0 [f]	212.5	340.0	1070.0	1190.0
Gut-wall	2.8 ± 0.5	154.6	119.0 [g]	204.0	255.0	714.0	833.0
Gut		262.8 [d]		357.0		1214.0	
Kidney	11.5 ± 1.4	19.3	97.1	42.5	170.0	214.0	952.0
Muscle	4.1 ± 0.5	1440.0	80.0 [h]	4250.0	170.0	21430.0	892.0
Fat	1.6 ± 0.5	154.6	7.3	1502.0 [j]	50.0 [j]	8714.0 [m]	179.0
Skin	3.3 ± 0.8	300.0	41.1	364.3 [l]	18.2 [l]	2143.0 [n]	107.0
Bone	2.9 ± 0.7	265.3 [e]	35.0 [i]	1214.3 [l]	21.9 [l]	7143.0 [n]	129.0
CL^{T}_{app}	(ml/min)	127 ± 10		340 ± 20		650 ± 120	
Excretion in urine (%)		12.0		5.0		10.0	

[a] From Harris and Gross, 1975 and Lin et al., 1982.
[b] From Wyler and Weisser, 1972.
[c] From Harrison and Gibaldi, 1977.
[d] Evaluated from the ratio of V_{GC}/V_{GW} in man.
[e] Subtract body weight from total other tissue's volume.
[f] Observed value in Table 1.
[g] $0.7 \times Q_{Li}$, assumed from man value.
[h] Bischoff and Dedrick, 1971.
[i] 7% of cardiac output (Jones, 1950).
[j] Chen and Andrade, 1976.
[k] Lutz et al., 1977.
[l] Evaluated from man values.
[m] Benowitz et al., 1974.
[n] Mapleson, 1963.

previously in rats. Clearly, the tissue-to-blood partition coefficients of rabbits were almost the same as those of rats.

Calculation based on the physiological pharmacokinetic model

Scheme 1 shows the physiological pharmacokinetic model utilized here for calculation. This model was built up on the basis of the following assumptions: (1) each tissue acts as a well-stirred compartment; (2) pentazocine distribution is limited by the blood flow rate; and (3) the tissue-to-blood concentration ratio of pentazocine is independent of the drug concentration.

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

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

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

where VB, BR, HT, LV, KD, MS, FT, SK and BN indicate the 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:

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

where AB and GW indicate the arterial blood and gut-wall, respectively.

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

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

where GC indicates the 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 neglected in this study, since the intestinal residue of the total pentazocine conjugated and unconjugated at 24 h after dosing was below 1% of the dose for the rabbit, almost the same as previously reported in rats (Ichimura et al., 1983). The rate constants k_{CW} and k_{WC} were assumed to have the same values of 0.05 min^{-1} as in the rat (Ichimura et al., 1983). In this simulation, the equations were deduced from the enterohepatic recirculation mechanism in which glucuronide pentazocine was completely and immediately hydrolyzed. The term of R_B (≈ 0.25) in Eqn. 7 means the ratio of the sum of conjugated and intact pentazocine excreted in the bile to total metabolites (subtracted 10% of dose as intact pentazocine excreated in the urine from dose administered) during 24 h after dosing, because intact and con-

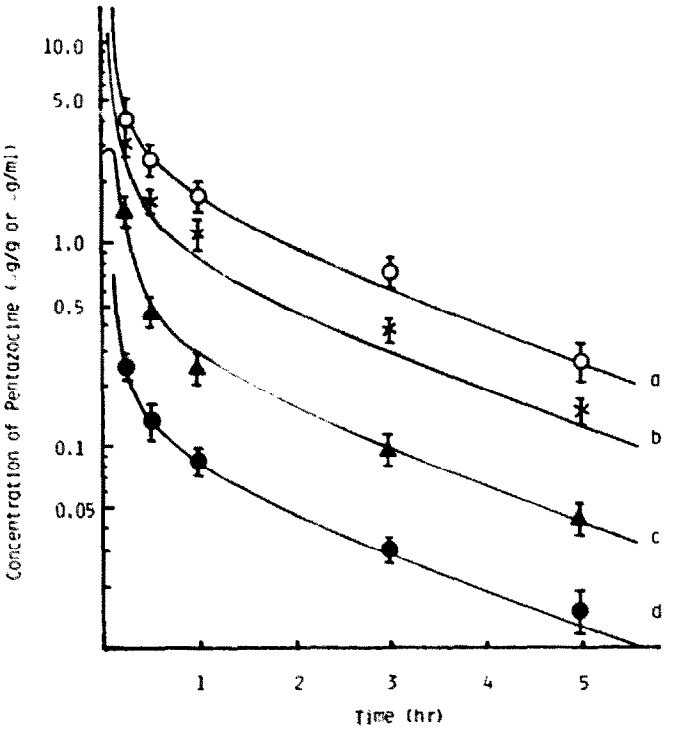


Fig. 2. Predicted and observed concentrations of pentazocine in tissues and in arterial blood after 1 mg/kg intravenous infusion over 2 min to unanesthetized rabbits. Key: a (○), lung; b (×), kidney; c (▲), brain; d (●), arterial blood. The observations represent the mean values ± S.D. from 3 animals.

jugated pentazocine excreted in the bile were below 0.5% and 23 ± 4% of dose, and intact and conjugated pentazocine excreted in the urine were 10 and 55–60% of dose, respectively.

Mass balance equations can be similarly given for the remaining compartments. In this simulation, the gastrointestinal absorption, renal clearance and hepatic clearance were assumed to be linear. No change in hepatic blood flow rate depending on the arterial concentration of pentazocine was assumed for the rabbit, dog at a dose below 3.5 mg/kg (Sone, 1979) or man at a dose below 2 mg/kg (Goto et al., 1977), in contrast to the previously described case of anesthetized rats.

The physiological parameters employed in this calculation are listed in Table 3. Thirteen differential equations were solved by the Runge-Kutta method using digital computer (FACOM M170F, Data Processing Center, Kanazawa University).

The model-predicted and observed pentazocine concentrations for the blood and various tissues after an intravenous dose of 1 mg/kg over 2 min to unanesthetized rabbits are shown in Figs. 2, 3 and 4. The stability test of the present model by comparing the numerical results derived from standard values for all parameters with ± 10% variation of standard values for each of the parameters. Such variation in any body region of the tissue volumes, and blood flow rate did not significantly affect the simulation results, indicating that model is quite stable within ± 10% of the physiological parameters.

The predicted and mean observed concentrations in the arterial blood after an

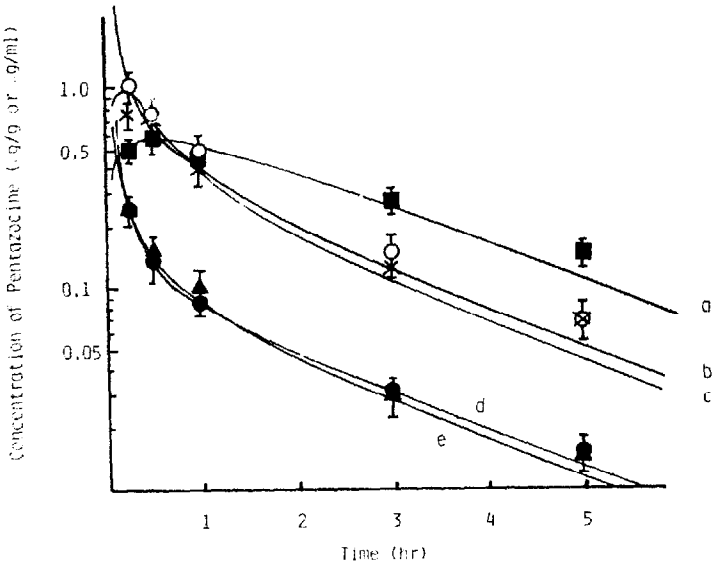


Fig. 3. Predicted and observed concentrations of pentazocine in tissues and in arterial blood after 1 mg/kg intravenous infusion over 2 min to unanesthetized rabbits. Key: a (■), muscle; b (○), gut-wall; c (×), bone; d (●), arterial blood; e (▲), liver. The observations represent the mean values ± S.D. from 3 animals.

intravenous dose of 0.5–10 mg/kg to rabbits are shown in Fig. 5. It was anticipated that model in the rabbit could be adapted for prediction in other animals including man, since all of the predictions in the rabbit made by using the same model as in the rat agreed well with the corresponding observed values.

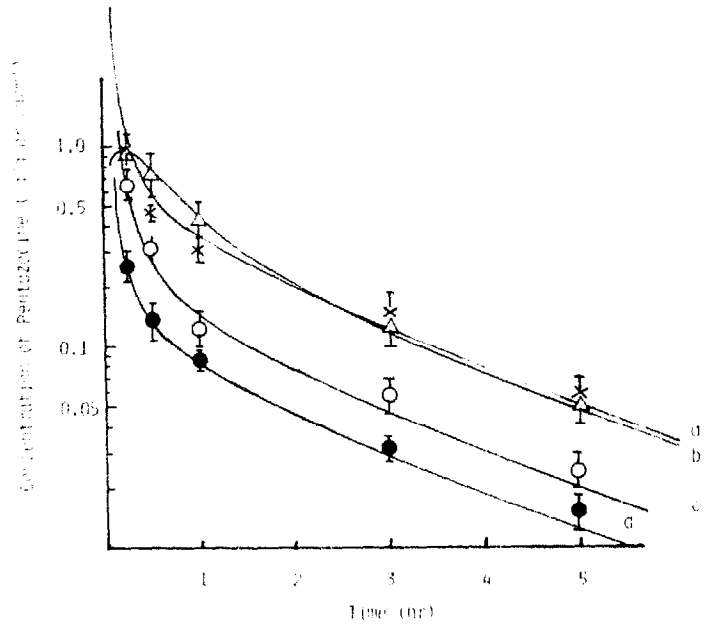


Fig. 4. Predicted and observed concentrations of pentazocine in tissues and in arterial blood after 1 mg/kg intravenous infusion over 2 min to unanesthetized rabbits. Key: a (×), heart; b (△), skin; c (○), fat; d (●), arterial blood. The observations represent the mean values ± S.D. from 3 animals.

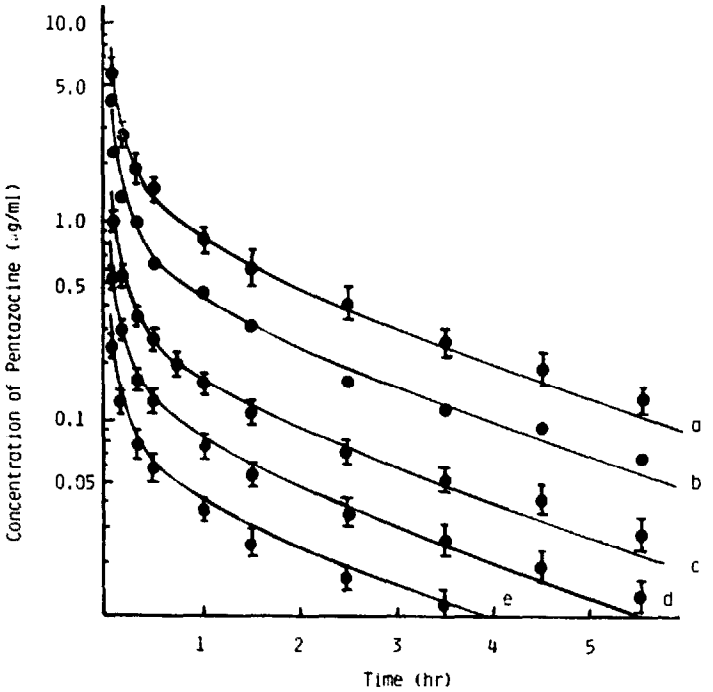


Fig. 5. Predicted and observed concentrations of pentazocine in arterial blood after a 0.5–10 mg/kg intravenous infusion over 2 min to unanesthetized rabbits. Key: a, 10 mg/kg; b, 5 mg/kg; c, 2 mg/kg; d, 1 mg/kg; e, 0.5 mg/kg. The observations represent the mean values ± S.D. from 3 animals (except in the case of the 5 mg/kg dose).

Simulation in beagle

Prediction of the venous blood concentration in beagles (n = 2) after a 3.5 mg/kg intravenous dose over 1 min was attempted using the present physiological model, the tissue-to-blood partition coefficients obtained in rabbits and other parameters for the beagle in Table 3. The CL_{app}^{KD} of pentazocine was calculated by dividing the amount of intact pentazocine excreted in urine during 24 h by AUC. CL_H was estimated by using Eqns. 2 and 4. Typical results are shown in Fig. 6. The predicted curve agreed well with the corresponding observed values.

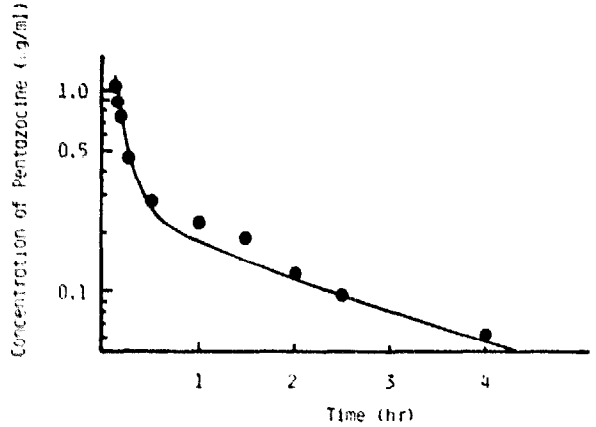


Fig. 6. Predicted and mean observed concentrations of pentazocine in venous blood after 3.5 mg/kg intravenous injection over 1 min to 2 beagles.

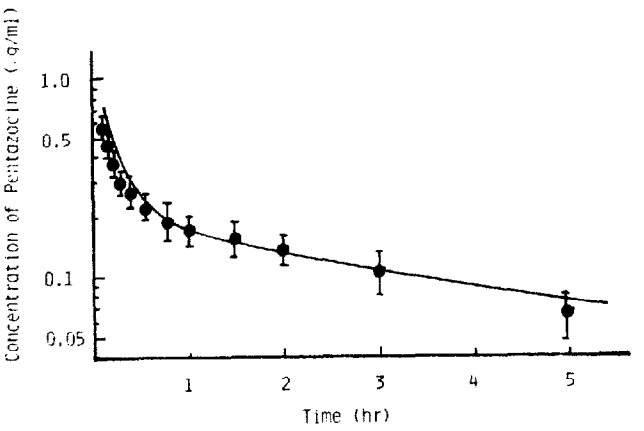


Fig. 7. Predicted and mean standard deviation of the observed concentration of pentazocine in venous plasma after 1 mg/kg intravenous injection over 1 min to patients. The observations represent the mean values ± S.D. from 5 patients.

Simulation in man

Prediction of the venous plasma concentration in man after a 1 mg/kg intravenous dose over 1 min was attempted using the physiological model, the tissue-to-blood partition coefficients obtained from rabbits and other parameters for man in Table 3. The clearance parameters were estimated by the same procedure as in beagles. The blood/plasma concentration ratio of pentazocine in man was about 1 (Ehrnebo et al., 1974). The results are shown in Fig. 7. All of the predictions agreed well with the corresponding mean observed values for 5 patients. The venous drug concentration declined more slowly than rabbits. It was clear that the model was useful for the prediction of the time course of pentazocine in man.

Additional dosage regimen for pentazocine in general anesthesia

For application of the method in the clinical situation, the additional dosage regimen for pentazocine was estimated. The main aim of this regimen was to maintain plasma pentazocine concentrations of above 0.2 μg/ml with minimal accumulation of pentazocine in any tissues. By the superposition principle, it seemed reasonable to assume that half of the initial dose of pentazocine could be given 60 min after the initial injection. Suitability of this regimen was confirmed by comparing the predicted and actual plasma pentazocine concentrations after an additional dose of pentazocine in 3 surgical patients. In these patients, 1 mg/kg pentazocine was administered intravenously as the initial dose followed by 0.5 mg/kg pentazocine intravenously as an additional dose. The results are illustrated in Fig. 8. Clearly, the predicted time-course of pentazocine in the plasma agreed well with the corresponding observed values. With this dosage regimen, the predicted brain concentration of pentazocine remains in a reasonable range in which the maximum concentration after the additional dose does not exceed that of the initial dose and the concentration after the additional dose is sustained during about 3 h at above the value just before the additional dosage, and there is no significant accumulation in

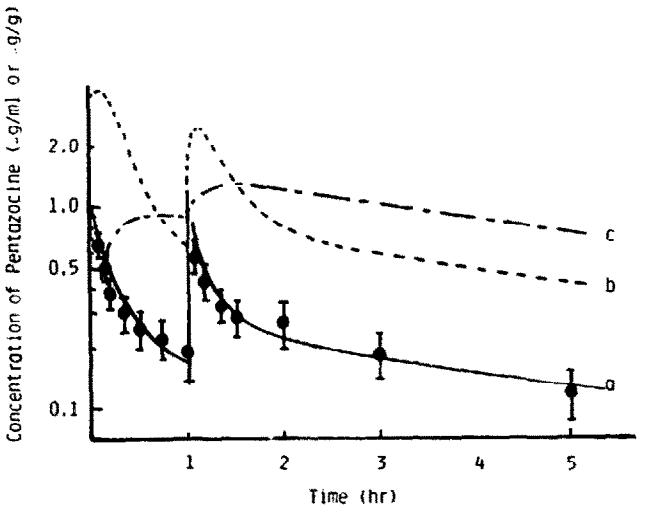


Fig. 8. Predicted and observed concentrations of pentazocine in venous plasma after 1 mg/kg intravenous injection followed by 0.5 mg/kg injection 1 h after the first dose over 1 min. Key: a (●———●), observed and predicted concentration in venous plasma; b (- - - - - -), predicted concentration in the brain; c (— · —), predicted concentration in muscle which is main accumlation tissue. The observation represents the mean values ± S.D. from 3 patients.

pentazocine depot tissue such as the muscle. For general anesthesia, this dosage regimen is in actual practical use at the Kanazawa University Hospital.

References

Agurell, S., Borèus, L.O., Gordon, E., Lindgren, J.E., Ehrnebo, E. and Lönroth, U., Plasma cerebrospinal fluid concentrations of pentazocine in patients: assay by mass fragmentography. J. Pharm. Pharmacol., 26 (1974) 1–8.

Arakawa, Y., Bandoh, M., Ogasawara, H., Tanaka, H., Nishida, N., Gotoh, Y. and Furukawa, K., Pharmacokinetics of pentazocine in dogs under nalothan anesthesia. Chem. Pharm. Bull., 27 (1979) 2217–2220.

Benowitz, N., Forsyth, R.P., Melmon, K.L. and Rowland, M., Lidocaine disposition kinetics in monkey and man. I. Prediction by a perfusion model. Clin. Pharmacol. Ther., 16 (1974) 87–98.

Bischoff, K.B. and Dedrick, R.L., Thiopental pharmacokinetics. J. Pharm. Sci., 57 (1968) 1346–1351.

Bischoff, K.B., Dedrick, R.L., Zaharko, D.S. and Longstreth, L.A., Methotrexate pharmacokinetics. J. Pharm. Sci., 60 (1971) 1128–1133

Chen, C.N. and Andrade, J.D., Pharmacokinetic model for simultaneous determination of drug levels in organs and tissues. J. Pharm. Sci., 65 (1976) 717–724.

Chen, H.S.G. and Gross, J.F., Estimation of tissue-to-plasma partition coefficient used in physiological pharmacokinetic model. J. Pharmacokin. Biopharm., 7 (1979) 117–125.

Ehrnebo, M., Agurell, S., Boreus, L.O., Gordon, E. and Lonroth, U., Pentazocine binding to blood cells and plasma protein. Clin. Pharmacol. Ther., 16 (1974) 424–429.

Ehrnebo, M., Boreus, L.O. and Lonroth, U., Bioavailability and first-pass metabolism of oral pentazocine in man. Clin. Pharmacol. Ther., 22 (1977) 888–893.

El-Mazati, A.M. and Way, E.L., The biologic disposition of pentazocine in the rat. J. Pharmacol. Exp. Ther., 177 (1971) 332–341.

Goto, T., Saito, Y., Kano, T. and Morioka, T., Mechanism of increase in arterial pressure after pentazocine Jap. J. Anesthesiol., 27 (1977) 239–245.

Harris, P.A. and Gross, J.F., Preliminary pharmacokinetic model for adriamycine (NSC-123127). Cancer Chemother. Rep., 59 (1975) 819–825.

Harrison, L.I. and Gibaldi, M., Physiologically based pharmacokinetic model for digoxin disposition in dogs and its preliminary application to humans. J. Pharm. Sci., 66 (1977) 1679–1683.

Ichimura, F., Yokogawa, K., Yamana, T., Tsuji, A. and Mizukami, Y., Physiological Pharmacokinetic model for pentazocine. I. Tissue distribution and elimination in the rat. Int. J. Pharm., 15 (1983) 321–333.

Ikeda, Y., Kasuya, H., Ozawa, H., Takagi, K., Takagi, H. and Fukuda, H., Studies on absorption, biotransformation and excretion of drug (6). The fate of pentazocine in the rat. Oyo Yakuri, 17 (1979) 179–187.

Jones, H.B., Medical Physics Chicago: Year Book, Vol. 2, 1950, p. 860.

Lutz, R.J., Galbraith, W.M., Dedrick, R.L., Shrager, R. and Mellett, L.B., A model for the kinetics of distribution of actinomycin-D in the beagle dog. J. Pharmacol. Exp. Ther., 200 (1977) 469–478.

Lin, J.H., Sugiyama, Y., Awazu, S. and Hanano, M., Physiological pharmacokinetics of ethoxybenzamide based on biochemical data obtained in vitro as well as on physiological data. J. Pharmacokin. Biopharm., 10 (1982) 649–661.

Mapleson, W.W., An electric analogue for uptake and exchange of inert gases and other agents. J. Appl. Physiol., 18 (1963) 197–204.

Neutze, J.M., Wyler, F. and Rudolph, A.M., Use of radioactive microspheres to assess distribution of cardiac output in rabbit. Amer. J. Physiol., 215 (1968) 486–495.

Pittman, K.A. and Portmann, G.A., Pharmacokinetics of pentazocine in the rhesus monkey. J. Pharm. Sci., 63 (1974) 84–88.

Sone, T., Study of cardiovascular effect of neuroleptanesthesia. Part I: Cardiovascular effect of pentazocine. Jap. J. Anesthesiol., 29 (1979) 225–231.

Stoeckel, K., McNamara, P.K., Mclean, A.J., duSouich, P., Lalka, D. and Gibaldi, M., Nonlinear pharmacokinetics of indocyanine green in the rabbit and rat. J. Pharmacokin. Biopharm., 8 (1980) 483–496.

Tsuji, A., Miyamoto, E., Terasaki, T. and Yamana, T., Physiological pharmacokinetics of β-lactam antibiotics: penicillin V distribution and elimination after intravenous administration in rat. J. Pharm. Pharmacol., 31 (1979) 116–119.

Tserlikkis, L., Ortega, E., Solomon, R. and Day, J.L., Pharmacokinetics of mercaptopurine. J. Pharm. Sci., 66 (1977) 1454–1457.

Vaughan, D.P. and Becket, A.H., An analysis of the inter-subject variation in the metabolism of pentazocine. J. Pharm. Pharmacol., 26 (1974) 789–798.

Wyler, F. and Weisser, K., Effect of halothane anaesthesia on distribution of cardiac output and organ blood flow in the rabbit. Br. J. Anaesthesiol., 44 (1972) 551–556.