J.Pharmacobio-Dyn., **8**, 757–766 (1985)

PREDICTION OF THE PLASMA CONCENTRATION TIME COURSES OF VARIOUS DRUGS IN HUMANS BASED ON DATA FROM RATS

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(Received February 4, 1985)

The concentrations of seven drugs, *i.e.*, phenobarbital (PB), phenytoin (DPH), hexobarbital (HXB), quinidine (QD), tolbutamide (TB), valproate (VA), and diazepam (DZP) in human plasma were predicted by a physiologically-based pharmacokinetic model using the intrinsic clearance of unbound drug and the tissue-to-plasma unbound concentration ratios extrapolated from rat data, and the plasma protein binding, blood-to-plasma concentration ratios and physiological parameters in humans. The predicted concentration curves of DPH, HXB, QD and PB in human plasma showed comparatively good agreements with the observed values except for TB, VA and DZP, for which the area under concentration-time curves (AUC) were overestimated or underestimated.

Keywords — animal scale-up; phenobarbital; phenytoin; hexobarbital; quinidine; tolbutamide; valproate; diazepam; physiological pharmacokinetic model

INTRODUCTION

There have been a number of reports dealing with interspecies variation in the drug metabolism and renal clearance.[1-7] Pharmacokinetic principle in the extrapolation of animal data to humans was applied by Boxenbaum[8-10] and Sawada *et al.*[11] Boxenbaum compared the metabolic intrinsic clearances (CLu_{int}) of antipyrine (AP), phenytoin (DPH), and benzodiazepines in humans with those in animal and found that CLu_{int} in humans was approximately one-seventh of that which would be predicted from other species.[8] Furthermore, he demonstrated an allometric relationship between CLu_{int} of AP, DPH and clonazepam per maximum lifespan potential and body weight, and suggested that man's lesser quantitative ability to metabolize many drugs may be correlated with his enhanced longevity.[9] Recently, Boxenbaum compared the pharmacokinetic parameters for 12 benzodiazepines in dog and humans, and simultaneously tried to make extrapolations from dog to humans.[10] Only recently, Sawada *et al.*[11] compared the pharmacokinetic parameters, *i.e.*, half-life ($t_{1/2,z}$), total body clearance (CL_P), renal clearance (CL_R), hepatic clearance (CL_H), volume of distribution (V), intrinsic clearance of unbound drug (CLu_{int}) and unbound volume of distribution of tissues (distributive tissue volume/fraction of drug in tissue unbound; V_T/fu_T) for six β-lactam antibiotics in mouse, rat, rabbits, dog, monkey and human, and two methods for extrapolation of animal to humans on the disposition of β-lactam antibiotics were presented. One was the Adolph-Dedrick approach, which can be used to predict clearances in humans from the relationship between CLu_{int} of unbound drug and the body weight in several animal species.[11] The other was the Boxenbaum approach, which might be able to predict pharmacokinetic parameters of β-lactam antibiotics using the regression line of a log-log plot on CLu_{int} and V_T/fu_T between one species (monkey) and humans.[11]

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In the previous study,[12] the literature was searched for pharmacokinetic data on nine weak acidic drugs, *i.e.*, DPH, hexobarbital (HXB), pentobarbital (PEB), warfarin (WA), tolbutamide (TB), valproate (VA), phenobarbital (PB), amobarbital (AB) and phenylbutazone (PBZ), and six weak basic drugs, *i.e.*, quinidine (QD), chlorpromazine (CPZ), propranolol (PL), pentazocine (PZ), diazepam (DZP) and AP. The Boxenbaum approach, which can predict pharmacokinetic parameters ($t_{1/2,z}$, V and CL_m) of various drugs using the regression line of a log-log plot on the CLu_{int} and V_T/fu_T between rat and human was investigated.[12] The predictions of $t_{1/2,z}$, V and CL_m in humans using rat data of the intrinsic parameters (V_T/fu_T and CLu_{int}) were successful for many drugs. Application of physiologically-based pharmacokinetics in the extrapolation of animal data to humans was reported by many investigators,[7,13-21] but little study has been done on the prediction of plasma concentration-time curves in humans using the intrinsic clearance and tissue distribution data in animal species.

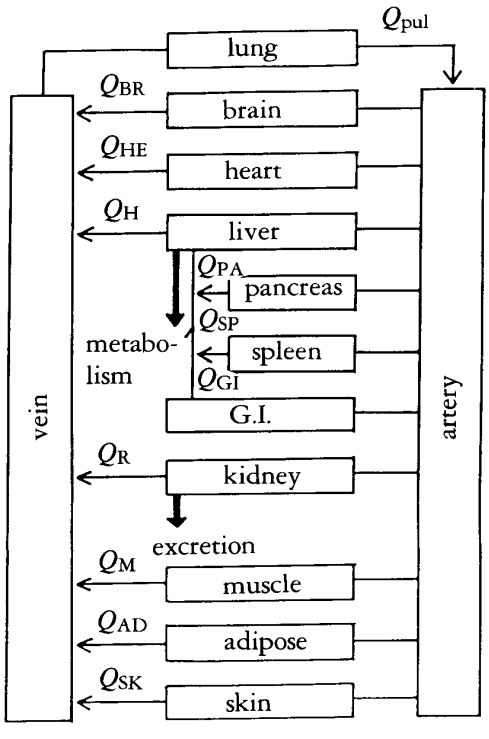
In the present study, the concentration-time curves of seven drugs, DPH, PB, HXB, QD, TB, VA and DZP in human plasma were predicted by a physiologically-based pharmacokinetic model using metabolic and tissue distribution parameters extrapolated from rat data, and parameters for the binding to blood components and physiological parameters in humans.

METHODOLOGY

The concentrations of seven drugs, *i.e.*, PB, DPH, HXB, QD, TB, VA and DZP, in human plasma were predicted by a physiologically-based pharmacokinetic model[22] using CLu_{int} and tissue-to-plasma unbound concentration ratios (Kpu) extrapolated from rat data, and plasma protein binding, blood-to-plasma concentration ratio (C_b/C) and physiological parameters in humans.

In our previous reports, the apparent volume of distribution after distribution equilibrium and the ratio of distributive tissue volume to the unbound fraction in the tissue (V_T/fu_T) of CPZ, imipramine, PL, disopyramide, lidocaine, QD, meperidine, PZ, chlorpheniramine, PBZ, DPH, HXB, TB, VA, DZP, PB, PEB, WA, AB, and methacyclin were compared in animal species and humans.[12,23] In two parameters, statistically significant correlation between animals and humans was obtained when the parameters were plotted on a log-log scale. The correlation coefficient between V_T/fu_T was significantly higher than that between the apparent volumes of distribution ($p < 0.05$). In general, there was little difference between V_T/fu_T of various basic drugs in animals and that of humans. The value of V_T/fu_T is expressed by the following equation.

$$\frac{V_T}{fu_T} = \sum_{i=1}^{n} Kpu_{T,i} V_{T,i} \quad (1)$$



Q: blood flow

FIG. 1. *Pharmacokinetic Model for the Disposition of Various Drugs in Humans*

The spleen and pancreas compartments were neglected for the simulation of the concentration profiles in PB, DPH, HXB, TB and DZP. The pancreas compartment was also neglected for the simulation of the concentration profiles in QD (see Text).

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where $V_{T,i}$ is the volume of i-th tissue (ml) and $Kpu_{T,i}$ is the tissue to plasma unbound concentration ratios in the i-th tissue. From these findings, we used the $Kpu_{T,}$ values of rats as those of humans.

Furthermore, we compared the metabolic clearance (CL_m) and intrinsic clearance of the unbound drug (CLu_{int}) for nine weak acidic and six weak basic drugs in rat and humans.[12] With regard to the two parameters, statistically significant correlations were obtained, when the parameters were plotted on a log-log plots. Correlation coefficients between the intrinsic parameters (CLu_{int}) was higher than that between the hybridized parameters (CL_m). Accordingly, the CLu_{int} of humans was calculated by substituting that of the rat into the following equation.[12]

$$(CLu_{int})_{human} = 0.130\,(CLu_{int})_{rat}^{0.953} \quad (2)$$

With regard to CL_R of PB and QD, the observed values in humans was utilized for the pharmacokinetic simulation. A physiologically based pharmacokinetic model for the distribution, disposition, and excretion of various drugs in humans is shown in Fig. 1. The complete set of differential equations is given in Appendix II and was solved numerically by the Runge-Kutta-Marson method.[24] Physiological constants used in the simulation for a 70-kg human are listed in Table I. Various parameters for plasma protein binding and metabolism of drugs used in the simulation are summarized in Table II. The *Kpu* of DPH,[25] TB,[22] DZP,[19] HXB,[26] PB,[26] VA[27] and QD[20] were obtained from the literatures.

RESULTS AND DISCUSSION

The recent development of anatomically and physiologically realistic pharmacokinetic models for drug disposition based on actual organ blood or plasma flows and physiological volumes[28-30] has made it possible to predict, in principle, the drug concentration in any tissue at any time and to provide considerable insight into drug dynamics. A further advantage of these models is that the drug disposition in disease states may be simulated by altering esti-

TABLE I. *Physiological Parameters for Modeling in 70 kg Adult Standard Human*

Tissue	Volume (ml)	Blood flow rate (ml/min)
Brain	1400[a]	700[a] (Q_{BR})
Lung	600[b]	4620[c] (Q_{pul})
Heart	300[b]	240[b] (Q_{HE})
Liver	3900[b]	1580[b] (Q_H)
Kidney	300[b]	1240[b] (Q_R)
G.I. tract	3180[d]	1100[d] (Q_{GI})
Muscle	30000[b]	600[b] (Q_M)
Skin	3000[b]	60[b] (Q_{SK})
Adipose tissue	10000[b]	200[b] (Q_{AD})
Spleen	200[d]	200[d] (Q_{SP})
Pancreas	200[e]	200[e] (Q_{PA})
Blood artery	1700[f]	
vein	3390[f]	

a) Obtained from ref. 43. b) Obtained from ref. 44. c) $Q_B + Q_{HE} + Q_H + Q_R + Q_M + Q_{SK} + Q_{AD}$. d) Obtained from ref. 45. e) Assumed to be equal to the value for spleen. f) Blood volume was calculated according to the report of Bischoff et al.[14] $V_p = 44 \times$ (body weight, kg)$^{0.99}$ $V_b = V_p/(1 -$ hematocrit), hematocrit $= 0.42$ The volume ratio of (artery blood)/(venous blood) was assumed to be the same as that for humans (i.e., 0.5).[15]

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TABLE II. *Parameters for Physiological Pharmacokinetic Simulation in Humans*

Kpu[a] and tissue binding parameters[b]	*Kpu*						*N*[b]	*Kd*[b]	*N*/*Kd*+1 [b]
	Phenytoin	Tolbutamide	Diazepam	Hexobarbital	Phenobarbital	Valproate	Quinidine		
Lung	3.52	1.09	22.5	5.27	1.09	0.588	94.2	0.270	350
Heart	3.54	0.767	15.1	1.81	1.30	0.687	39.0	1.43	28.3
Liver	10.6	0.551	33.7	9.63	2.57	1.12	31.9	0.0400	799
G.I. tract	5.15	0.324	12.8	2.04	2.22	1.25	27.4	0.470	59.3
Kidney	5.15	0.537	15.9	2.44	1.04	1.13	169	2.90	59.3
Muscle	2.77	0.339	9.44	1.01	1.40	0.331	14.9	0.840	18.7
Skin	4.33	0.784	23.2	1.47	1.71	1.87	14.6	0.65	22.5
Adipose tissue	4.85	0.465	88.9	2.65	0.425	0.314	8.40	1.11	7.57
Brain	3.98	0.155	7.03	1.63	1.901	0.339	7.90	1.77	4.46
Pancreas	—[c]	0.400	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Spleen	—[c]	0.595	—[c]	—[c]	—[c]	0.481	100	0.85	119
fu[d]	0.120	0.093	0.032	0.534	0.543	0.113		0.230	
C_b/C[d]	0.610	0.752	1.04	1.00	0.861	0.28		0.92	
$CLu_{int,H}$ (ml/min/kg)[e]	4.15	0.635	72.2	9.55	0.152	1.44		16.4	
CL_R (ml/min/kg)	0.00	0.00	0.00	0.00	0.0139[f]	0.00		1.58[f]	
$CL_{int,R}$ (ml/min/kg)					0.0256[g]			7.61[g]	
Dose (mg/kg)	2.00	15.4	0.100	7.37	1.91	6.25		4.00—5.00	

a) The tissue-to-plasma unbound concentration ratios (Kpu) were obtained from the literatures, i.e. phenytoin (DPH),[25] tolbutamide (TB),[22] diazepam (DZP),[19] hexobarbital (HXB),[26] phenobarbital (PB),[26] valproate (VA),[27] and quinidine (QD).[20] b) Non-linear tissue distribution of quinidine was reported by Harashima et al.[20] N (μg/ml) and Kd (μg/ml) are the binding capacity and dissociation constant, respectively. c) Not determined. d) The plasma unbound fraction (fu) and the blood-to-plasma concentration ratio (C_b/C) of human were obtained from the literatures, i.e., DPH,[46,47] TB,[48] DZP,[4] HXB,[49,50] PB,[51–53] VA,[54] and QD.[55,56] e) The metabolic intrinsic clearance of unbound drug ($CLu_{int,H}$) predicted using those in the rat. See the text for detail. f) The values of renal clearance (CL_R) of human were obtained from the literatures, i.e., PB,[51] and QD.[55] g) The values of the real unbound intrinsic clearance ($CLu_{int,R}$) of human were calcualted by the equation:

$$CLu_{int,R} = \frac{CL_R Q_R}{fu\,(Q_R - CL_R)}$$

mates of organ blood flow,[15,31] metabolic clearance of the drug, urinary or biliary clearance of the drug,[32] or plasma and tissue binding of the drug. Furthermore, the most important application is interspecies scale-up, where the large data base required to develop a physiological pharmacokinetic model may be determined in a laboratory animal and scaled up to apply to humans. This approach has been applied successfully to predict the disposition of thiopental,[13] methotrexate,[14] 1-β-D-arabionofuranosylcytosine,[7] lidocaine,[15] sulfobromophthalein,[16] adriamycin,[17] digoxin,[18] β-lactam antibiotics,[33,34] PZ,[35] DZP,[19] and QD.[20]

The tissue-to-plasma unbound concentration ratios (*Kpu*) were calculated by the following

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equation and are listed in Table II:

$$Kpu_{T,i} = \frac{C_{T,i}}{Cu} = \frac{Kp_{T,i}}{fu} \cdot \frac{C_b}{C} \quad (3)$$

where T, i represents all tissues studied. Various drugs showed characteristic tissue distributions with respect to their magnitude and marked differences in the *Kpu* values among tissues. The *Kpu* values of basic drugs such as QD and DZP were larger than those of acidic drugs such as DPH, TB, HXB, PB and VA. The characteristic tissue distribution of QD and DZP may be explained by their extensive tissue bindings.[20] The *Kpu* values of TB and VA were not greater than one in any tissue studied. The unusual tissue distribution of these drugs in rat may be attributed to several possible mechanisms, such as pH differences between the intra- and extracellular fluids,[36] existence of intracellular space which is impermeable to these drugs, and heterogenous distribution of drugs in the tissue.

Twelve or thirteen differential equations (see Appendix II) were solved by the Runge-Kutta-Marson method using parameters listed in Tables I and II. The predicted plasma concentration time courses of various drugs after *i.v.* administration are shown in Figs. 2 and 3. The concentration-time course of various drugs in tissues or organs calculated simultaneously with those in plasma was not shown here because of the lack of observed data for the comparison. Comparatively good agreements were obtained

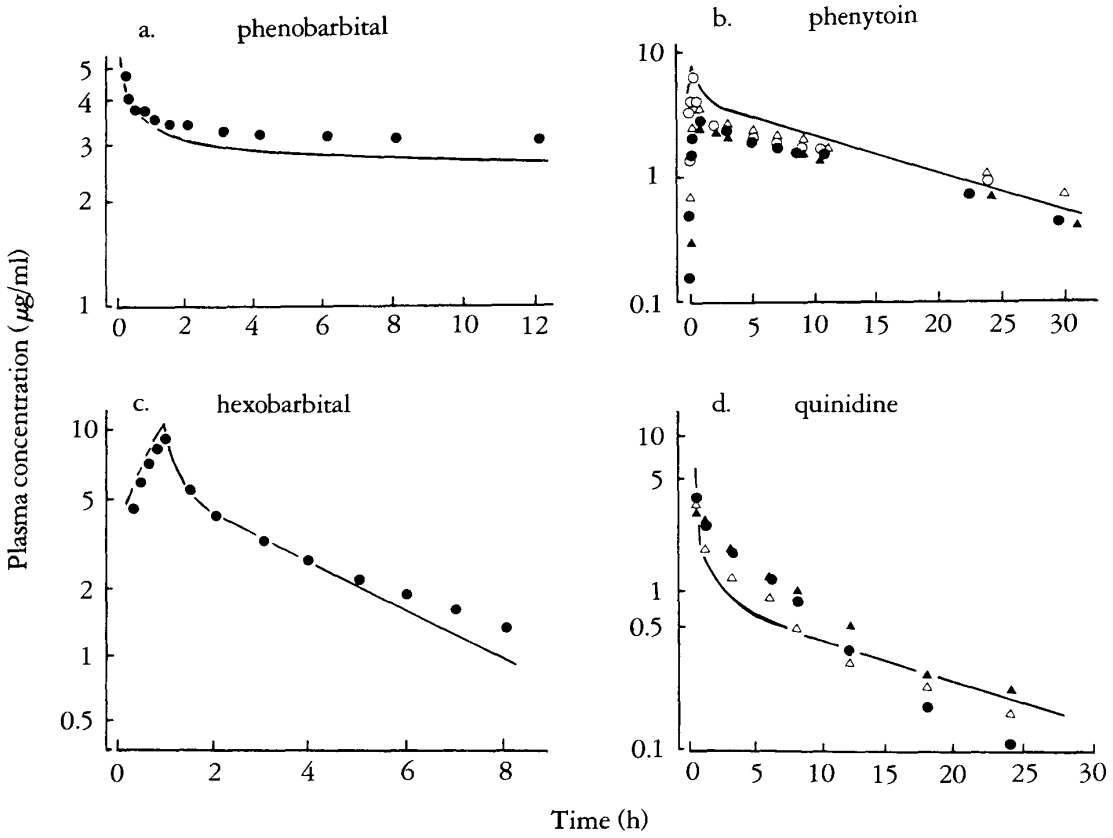

FIG. 2. *Predicted and Observed log Plasma Concentrations of Various Drugs after i.v. Administration in Humans*

(a) phenobarbital (PB), (b) phenytoin (DPH), (c) hexobarbital (HXB), (d) quinidine (QD). Key: (●, ○, ▲, △) data of each subject, and (——) predicted concentration of various drugs. Observed values were obtained from the literatures for PB,[51] DPH,[46] HXB[49] and QD.[55]

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between the predicted and observed plasma concentrations of PB, DPH, HXB and QD in humans (Fig. 2), while a discrepancy during the terminal phase was observed for TB, VA and DZP (Fig. 3). This seemed to be due to an underestimation of CLu_{int} of TB and an overestimation of CLu_{int} for VA and DZP. The difference in TB may be due to the human data from the diabetic and that in VA may be due the interspecies difference in metabolism process, namely in rats VA is extensively metabolized by oxidation while in humans by glucuronidation. The large difference in CLu_{int} for DZP between rat and humans may be due to that in the metabolic process. At present time, we cannot clear the primary factor. This finding may imply a limitation of using Eq. 2 in order to predict the CLu_{int} for some drugs in humans from that in an animal. However, the predictions for V seemed to be successful, because the simulated plasma concentration at initial distribution phase agreed with the observed values.

In the extrapolation of human pharmacokinetic parameters from animal data, the interindividual difference is most important. However, in the case of WA,[37,38] PL,[39] QD,[40] and DPH,[41] a good relationship was observed between V (or CL) and fu (or fu_s). Therefore, V_T/fu_T and CLu_{int} did not show a large interindividual difference and so fu is the primary factor of the interindividual difference in V (or V_{ss}) and CL_m. Thus, the interindividual difference seems not to be the primary factor of the variation in the intrinsic parameters.

Another probrem is the variation in Q_H. In rats, in the case of the high intrinsic clearance (for example, HXB and DZP) the value of CLu_{int} is changed in the range of 2—4 times by +/— 30% change of Q_H. The extrapolation of this rat value to the CL for humans may result in the low predictability. On the other hand, the drug of which CLu_{int} for rats is low, shows also low values of CLu_{int} for humans and therefore both values of CL for rat and humans may be little affected by Q_H.

In the future, the precision of predictions from data from many species may become higher than that obtained using data from one species only, as in the present study.

In conclusion, our proposed approach in the present paper might be useful for developing insight into the prediction of plasma and tissue concentration-time courses in humans.

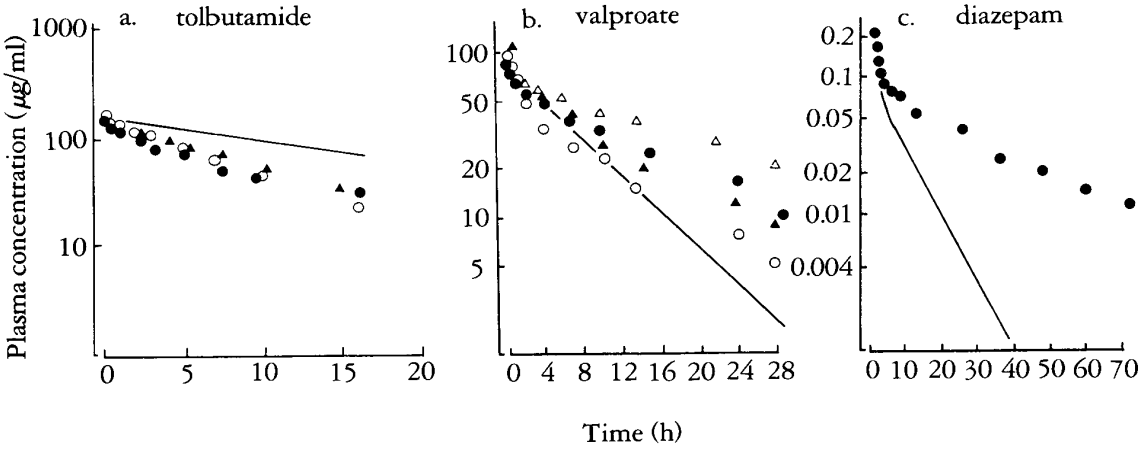

FIG. 3. *Predicted and Observed log Plasma Concentrations of Various Drugs after i.v. Administration in Humans*

(a) tolbutamide (TB), (b) valproate (VA), (c) diazepam (DZP). Key: (●, ○, ▲, △) data of each subject, and (——) predicted concentration of various drugs. Observed values were obtained from the literatures for TB,[48] VA,[54] and DZP.[4]

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APPENDIX I: NOMENCLATURE

General

V : volume of distribution at terminal phase (ml)
V_{ss} : volume of distribution at steady state (ml)
$V_{T,i}$: tissue or organ volume of i-th tissue or organ (ml)
V_p : plasma volume (ml)
V_b : blood volume (ml)
$Kpu_{T,i}$: tissue-to-plasma unbound concentration ratio of i-th tissue or organ
$Kp_{T,i}$: tissue-to-plasma concentration ratio of i-th tissue or organ
CL_p : plasma clearance (ml/min/kg)
CL_m : metabolic clearance (ml/min/kg)
CL_H : hepatic clearance (ml/min/kg)
CL_R : renal clearance (ml/min/kg)
CLu_{int} : intrinsic clearance of unbound drug (ml/min/kg)
$CLu_{int,H}$: hepatic intrinsic clearance of unbound drug (ml/min/kg)
$CLu_{int,R}$: renal intrinsic clearance of unbound drug (ml/min/kg)
C_b : blood concentration of drug (μg/ml)
C : plasma concentration of drug (μg/ml)
Cu : unbound concentration of drug (μg/ml)
C_b/C : blood-to-plasma concentration ratio
fu : plasma unbound fraction
fu_s : serum unbound fraction
fu_T : tissue unbound fraction
D : dose
θ : reciplocal of injection time (ml^{-1})
R_0 : infusion rate (ml/min/kg)
$I(t)$: injection function
$t_{1/2,z}$: half life at terminal phase (min)
AUC : area under concentration-time curve ((μg/ml) $\cdot$min)
PB : phenobarbital
DPH : phenytoin
HXB : hexobarbital
QD : quinidine
TB : tolbutamide
VA : valproate
DZP : diazepam

Subscripts

b : blood
A : artery
V : vein
HE : heart
G.I. : gastro-intestine
SK : skin
PA : pancreas
AD : adipose
P : plasma
pul : lung
BR : brain
M : muscle
H : liver
SP : spleen
R : kidney
T, i : i-th tissue or organ

APPENDIX II: MODEL EQUATIONS

The following mass balance blood flow equations describe the drug concentration in each compartment of the pharmacokinetic model shown in Fig. 1.

Artery blood:

$$V_A\, dC_A/dt = (C_{pul}/Kpu_{pul} - C_A) \cdot Q_{pul} \quad (4)$$

Venous blood:

$$V_V\, dC_V/dt = C_{BR}\, Q_{BR}/Kp_{BR} + C_{HE}\, Q_{HE}/Kp_{HE} + C_H\, Q_H/Kp_H + C_R\, Q_R/Kp_R + C_M\, Q_M/Kp_M + C_{SK}\, Q_{SK}/Kp_{SK} + C_{AD}\, Q_{AD}/Kp_{AD} + I(t) \quad (5)$$

Lung:

$$V_{pul}\, dC_{pul}/dt = (C_V - C_{pul}/Kp_{pul}) \cdot Q_{pul} \quad (6)$$

Liver:

$$V_H\, dC_H/dt = (Q_H - Q_{GI} - Q_{PA} - Q_{SP}) \cdot C_A + C_{GI}\, Q_{GI}/Kp_{GI} + C_{SP}\, Q_{SP}/Kp_{SP} + C_{PA}\, Q_{PA}/Kp_{PA} - C_H\, Q_H/Kp_H - CLu_{int,H}\, C_H/Kp_H \quad (7)$$

Kidney:

$$V_R\, dC_R/dt = (C_A - C_R/Kp_R) \cdot Q_R - CLu_{int,R}/Kpu_R \quad (8)$$

Non-eliminating organ and tissue:

$$V_{T,i}\, dC_{T,i}/dt = (C_A - C_{T,i}/Kp_{T,i}) \cdot Q_{T,i} \quad (9)$$

where subscripts A, pul, V, BR, HE, M, SK, H, GI, SP, PA, R, AD, and T, i denote the artery, lung, vein, brain, heart, muscle, skin, liver, gas-

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tro-intestinal tract, spleen, pancreas, kidney, adipose tissue and non-eliminating oragn or tissue, respectively. D is the dose and $I(t)$ is the injection function given by

For TB, DZP, PB and VA

$$I(t) = D \cdot \theta\,(\theta t)^2(1-\theta t)^2$$

(D: dose; $\theta = 10\ \text{min}^{-1}$)[42]

For DPH and HXB

$I(t) = R_0$; $R_0 = 0.107$ mg/min/kg, $0 < t \leqq 18.7$ min (DPH), and $R_0 = 0.123$ mg/min/kg, $0 < t \leqq 60.0$ min (HEB), respectively.

Tissue-to-blood partition coefficients (Kp) in eqs. 4–9 were calculated by

$$Kp_{T,i} = (C/C_b) \cdot fu \cdot Kpu_{T,i} \qquad (10)$$

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