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A Pharmacokinetic Model for Simulating Drug Concentrations in Tissues or Fluids and Its Application to Antibiotics

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Drugs administered *in vivo* are transferred directly or indirectly from blood to tissues or fluids, and *vice versa*. In this paper, we propose a model by which the drug concentration in tissues or fluids can be analyzed simply by using a transfer rate constant and apparent clearance ratio, regardless of the transfer route. By using this model, the concentration-time curves of antibiotics in pleural effusion, burn blister fluid and aqueous humor of human subjects were successfully analyzed.

Keywords—pharmacokinetic analysis; modified two-compartment model; modified three-compartment model; transfer rate constant; apparent clearance ratio; pharmacokinetic profile; pleural effusion; burn blister fluid; aqueous humor; geometrical mean

Pharmacokinetic behavior of drug absorption and disposition is usually analyzed based on plasma concentration data. However, it is also important in the clinical application of a drug to investigate the drug levels in various tissues or body fluids and to elucidate the relationship between drug concentration in plasma and that in these tissues or fluids. Previously, as a part of a study on infectious disease in the field of obstetrics and gynecology, we reported that sulbenicillin levels in the reproductive organs following a constant rate infusion could be successfully analyzed by using a three-compartment open model, assigning plasma, ovary and oviduct, and exudate of dead space to the first, the second, and the third compartments, respectively.¹⁾ Thereafter, several similar studies on the analysis of drug concentration in body fluids and tissues after administration of antibiotics have been reported, mainly in the field of obstetrics and gynecology,²⁾ to evaluate the clinical utility of new antibiotic agents for the treatment or prevention of infections during and after operation. Recently, drug concentrations in pleural effusion,³⁾ burn blister fluid,⁴⁾ and aqueous humor after intravenous injection of antibiotic agents have also been analyzed pharmacokinetically in the fields of thoracic and cardiovascular surgery, plastic surgery, and ophthalmology, respectively. However, there has been no consistency in the methods used for pharmacokinetic analyses, and in some reports the analyses were carried out merely with plural exponential terms, regardless of the plasma concentration-time course. Although our previously reported method¹⁾ had the advantage that drug concentrations in body fluids and tissues were correlated to those in plasma or serum, it also had the disadvantage that drug concentrations in ovary, oviduct and exudate of dead space were excessively reflected to the plasma concentration-time course. In order to overcome this disadvantage, a method^{4b)} was considered in which drug concentrations in tissues and fluids were analyzed by using a transfer rate constant and apparent clearance ratio from blood to a certain tissue or fluid without changing the pharmacokinetic parameters⁵⁾ obtained from the analysis of plasma concentration data, which could be measured precisely. Even by this method, it is impossible to analyze the drug concentration data in such a fluid as the aqueous humor⁶⁾ into which drugs are transferred indirectly from the blood.

In the present paper we wish to propose a model by which drug concentrations in tissues or fluids can be simply analyzed regardless of the transfer route, and to present some successful examples of analysis by this new method of drug concentrations in tissues and fluids following intravenous injection of antibiotics.

Pharmacokinetic Model for Simulating Drug Concentrations in Tissues or Fluids

Provided that a drug administered *in vivo* is transferred from blood to tissues or fluids by passive transport, the drug concentrations in tissues or fluids can be represented by those in the second compartment of the modified two-compartment model illustrated in Fig. 1 or the third compartment of the modified three-compartment model in Fig. 2. The central (plasma) compartment of the usual two-compartment open model is shown as compartment 1 in Figs. 1 and 2, and the peripheral compartment is not shown. Instead, an additional compartment corresponding to a tissue or fluid is linked directly to the plasma compartment in Fig. 1, and linked indirectly to the plasma compartment through the intermediate one in Fig. 2. In Figs. 1 and 2, Q_i , C_i and V_i represent the amount, concentration and distribution volume of drug in compartment i , respectively, while k_1 and k_{-1} , and k_2 and k_{-2} are the transfer rate constants between compartments 1 and 2, and compartments 2 and 3, respectively. The change in the amount of the drug in the tissue or fluid to which the drug is transferred directly from the blood, *i.e.*, that in compartment 2 of Fig. 1, is expressed by Eq. 1. The change of drug

$$\frac{dQ_2}{dt} = k_1 Q_1 - k_{-1} Q_2 \tag{1}$$

$$\frac{dC_2}{dt} = k_{-1}(F_1 C_1 - C_2) \tag{2}$$

$$F_1 = k_1 V_1 / k_{-1} V_2$$

concentration is given by Eq. 2, using an apparent clearance ratio F_1 from the blood to the tissue or fluid. On the other hand, the plasma concentration–time course based on the usual

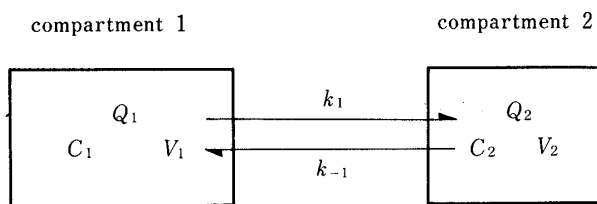


Fig. 1. Schematic Diagram of the Modified Two-Compartment Model

Q_1, C_1, V_1 : amount, concentration and distribution volume of drug in compartment 1 (blood).
 Q_2, C_2, V_2 : amount, concentration and distribution volume of drug in compartment 2 (a certain tissue or fluid).
 k_1, k_{-1} : transfer rate constants between compartment 1 and 2.

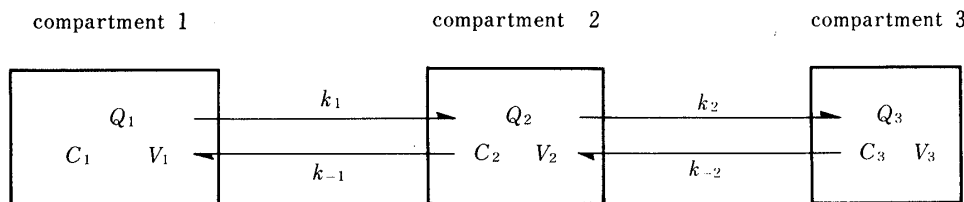


Fig. 2. Schematic Diagram of the Modified Three-Compartment Model

Q_1, C_1, V_1 : amount, concentration and distribution volume of drug in compartment 1 (blood).
 Q_2, C_2, V_2 : amount, concentration and distribution volume of drug in compartment 2 (intermediate compartment).
 Q_3, C_3, V_3 : amount, concentration and distribution volume of drug in compartment 3 (a certain tissue or fluid).
 k_1, k_{-1}, k_2, k_{-2} : transfer rate constants between compartments 1 and 2, and compartments 2 and 3.

two-compartment open model following bolus intravenous injection is given by the well-known Eq. 3. In Eq. 3, α , β , k_{21} , V_1 and D represent the rate constants of the α - and β -phase, transfer

$$C_1 = A_{11}e^{-\alpha t} + A_{12}e^{-\beta t} \quad (3)$$

$$A_{11} = \frac{\alpha - k_{21}}{\alpha - \beta} \frac{D}{V_1}, \quad A_{12} = \frac{k_{21} - \beta}{\alpha - \beta} \frac{D}{V_1}$$

rate constant from the peripheral to the central compartment, apparent volume of distribution in the central compartment and amount of drug administered, respectively. Integration of Eq. 2 after substitution of Eq. 3 into Eq. 2 leads to Eq. 4. The F_1 value is theoretically equal

$$C_2 = F_1(A_{21}e^{-\alpha t} + A_{22}e^{-\beta t} + A_{23}e^{-k_{-1}t}) \quad (4)$$

$$A_{21} = k_{-1}A_{11}/(k_{-1} - \alpha), \quad A_{22} = k_{-1}A_{12}/(k_{-1} - \beta)$$

$$A_{23} = -(A_{21} + A_{22}) = k_{-1}(k_{21} - k_{-1})D/(\alpha - k_{-1})(\beta - k_{-1})V_1$$

to AUC_2/AUC_1 , which is the ratio between the area under the drug concentration–time curve in the tissue or fluid and that in the plasma. On the other hand, drug concentration in compartment 3 shown in Fig. 2 is expressed by Eq. 5, on the assumption that the contribution

$$C_3 = F_2(A_{31}e^{-\alpha t} + A_{32}e^{-\beta t} + A_{33}e^{-k_{-1}t} + A_{34}e^{-k_{-2}t}) \quad (5)$$

$$F_2 = k_1k_2V_1/k_{-1}k_{-2}V_3$$

$$A_{31} = k_{-2}A_{21}/(k_{-2} - \alpha), \quad A_{32} = k_{-2}A_{22}/(k_{-2} - \beta)$$

$$A_{33} = k_{-2}A_{23}/(k_{-2} - k_{-1})$$

$$= k_{-1}k_{-2}(k_{21} - k_{-1})D/(\alpha - k_{-1})(\beta - k_{-1})(k_{-2} - k_{-1})V_1$$

$$A_{34} = -(A_{31} + A_{32} + A_{33})$$

$$= k_{-1}k_{-2}(k_{21} - k_{-2})D/(\alpha - k_{-2})(\beta - k_{-2})(k_{-1} - k_{-2})V_1$$

from compartment 3 to drug concentration in compartment 2 is negligibly small compared with that from compartment 1. F_2 in Eq. 5 is the apparent clearance ratio from compartment 1 to compartment 3. When the plasma concentration–time course is available, C_3 can be expressed by a function of k_{-1} , k_{-2} and F_2 . However, when k_{-1} , k_{-2} and F_2 are evaluated in practice so as to fit the calculated values from Eq. 5 with the observed drug concentrations in a tissue or fluid, the values of k_{-1} and k_{-2} are not determined unequivocally, though the value of F_2 is obtained accurately, since the drug concentration in the intermediate compartment is unavailable. That is, several solutions are obtained for k_{-1} and k_{-2} to minimize the sum of weighted squares of differences between the observed and the calculated values, and the products of k_{-1} and k_{-2} tend to be close to each other. When it is not clear which compartment (2 in Fig. 1 or 3 in Fig. 2), a tissue or fluid belongs to, a better pharmacokinetic profile can be obtained using Eq. 5 rather than Eq. 4, since more parameters are used in Eq. 5. The analysis with Eq. 5 is not necessarily more reasonable than that with Eq. 4. In order to analyze drug concentrations using three exponential terms with two unknown parameters (F_2 , and k_{-1} or k_{-2}), a condition is required such that either the coefficient A_{33} or A_{34} in Eq. 5 becomes zero. In Eq. 5, A_{33} becomes zero when k_{-1} is equal to k_{21} . Substitution of the relationship of $k_{-1} = k_{21}$ into Eqs. 4 and 5 leads to Eqs. 6 and 7, respectively. Equation 6

$$C_2 = F_1(A_{21}e^{-\alpha t} + A_{22}e^{-\beta t}) \quad (6)$$

$$A_{21} = -A_{22} = -k_{21}D/(\alpha - \beta)V_1$$

$$\begin{aligned}
 C_3 &= F_2(A_{31}e^{-\alpha t} + A_{32}e^{-\beta t} + A_{34}e^{-k_{-2}t}) & (7) \\
 A_{31} &= k_{21}k_{-2}D/(\alpha - \beta)(\alpha - k_{-2})V_1 \\
 A_{32} &= k_{21}k_{-2}D/(\alpha - \beta)(k_{-2} - \beta)V_1 \\
 A_{34} &= k_{21}k_{-2}D/(\alpha - k_{-2})(\beta - k_{-2})V_1
 \end{aligned}$$

indicates that the intermediate compartment kinetics exactly parallel those of the drug in the peripheral compartment of the usual two-compartment open model. Therefore, Eq. 7 may be taken as the equation that represents the drug concentration in a tissue or fluid to which the drug is transferred through the peripheral compartment of the usual two-compartment open model. On the other hand, when k_{-2} is equal to k_{21} , A_{34} in Eq. 5 becomes zero. In this case, C_3 is expressed by an equation where k_{-2} and A_{34} in Eq. 7 are substituted by k_{-1} and A_{33} , respectively. Under the limitation that either k_{-1} or k_{-2} is equal to k_{21} , the drug concentration in the third compartment of Fig. 2 can be analyzed with the three-exponential equation, Eq. 7. The characteristic difference between Eqs. 4 and 7 is that the slope of the concentration-time curve is zero at $t=0$ in Eq. 7. Therefore, it is reasonable to use Eq. 7 for the analysis of drug concentrations in a tissue and/or fluid where the concentration gradually rises after administration.

In the case that drug concentrations in the intermediate compartment are available, the use of Eq. 5 would be reasonable.

In the case of constant-rate intravenous infusion, the equations corresponding to Eqs. 4 and 7 are Eqs. 8 and 9, respectively, where K is the constant infusion rate, t_0 is the infusion time and t' represents the time since the end of infusion.

$$\begin{aligned}
 C_2 &= F_1\{A_{21}^*(1 - e^{-\alpha t}) + A_{22}^*(1 - e^{-\beta t}) + A_{23}^*(1 - e^{-k_{-1}t})\} & (0 \leq t \leq t_0) \\
 &= F_1\{(1 - e^{-\alpha t_0})A_{21}^*e^{-\alpha t'} + (1 - e^{-\beta t_0})A_{22}^*e^{-\beta t'} + (1 - e^{-k_{-1}t_0})A_{23}^*e^{-k_{-1}t'}\} & (t \geq t_0) & (8) \\
 A_{21}^* &= k_{-1}(\alpha - k_{21})K/(\alpha - \beta)(k_{-1} - \alpha)\alpha V_1 \\
 A_{22}^* &= k_{-1}(k_{21} - \beta)K/(\alpha - \beta)(k_{-1} - \beta)\beta V_1 \\
 A_{23}^* &= (k_{21} - k_{-1})K/(\alpha - k_{-1})(\beta - k_{-1})V_1
 \end{aligned}$$

$$\begin{aligned}
 C_3 &= F_2\{A_{31}^*(1 - e^{-\alpha t}) + A_{32}^*(1 - e^{-\beta t}) + A_{34}^*(1 - e^{-k_{-2}t})\} & (0 \leq t \leq t_0) \\
 &= F_2\{(1 - e^{-\alpha t_0})A_{31}^*e^{-\alpha t'} + (1 - e^{-\beta t_0})A_{32}^*e^{-\beta t'} + (1 - e^{-k_{-2}t_0})A_{34}^*e^{-k_{-2}t'}\} & (t \geq t_0) & (9) \\
 A_{31}^* &= k_{21}k_{-2}K/(\alpha - \beta)(\alpha - k_{-2})\alpha V_1 \\
 A_{32}^* &= k_{21}k_{-2}K/(\alpha - \beta)(k_{-2} - \beta)\beta V_1 \\
 A_{34}^* &= k_{21}K/(\alpha - k_{-2})(\beta - k_{-2})V_1
 \end{aligned}$$

Results

1) Pharmacokinetic Profile of Cefotiam (CTM) Concentration in Pleural Effusion

The CTM concentration data reported in experimental and clinical studies of CTM in thoracic surgery^{3a)} were used for the pharmacokinetic analysis. Blood and pleural effusion samples were collected simultaneously from 6 patients undergoing thoracic surgery at 1.0, 2.0, 3.0, 4.0 and 8.0 h after the start of the 1 h intravenous drip infusion of 1 g of CTM. First, the serum concentration data were analyzed with the usual two-compartment open model to afford the pharmacokinetic parameters listed in Table I. Subsequently, the values of V_1 , α , β and k_{21} obtained from individual patients were substituted into Eqs. 8 and 9, and the optimum values of k_{-1} and F_1 and those of k_{-2} and F_2 were determined by the combined use of the least-squares method and steepest-descent method to minimize the sum of the weighted

TABLE I. Pharmacokinetic Parameters Obtained from the Serum CTM Levels of Patients Undergoing Thoracic Surgery ($n=6$)

Parameters	Arithmetic Mean \pm S.D.	Geometrical Mean
α (h^{-1})	3.02 ± 0.79	2.93
β (h^{-1})	0.59 ± 0.11	0.58
$t_{1/2\beta}$ (h)	1.21 ± 0.19	1.19
V_1 (l)	12.3 ± 4.0	11.8
V_d (l)	38.4 ± 13.9	36.2
Cl (ml/min)	368 ± 116	352
AUC ($\mu\text{g}\cdot\text{h}/\text{ml}$)	49.6 ± 16.6	47.4
k_{21} (h^{-1})	1.00 ± 0.35	0.96

S.D. = standard deviation.

TABLE II. Pharmacokinetic Parameters Obtained from the Concentrations of CTM in Pleural Effusion ($n=6$)

Parameters	Arithmetic Mean \pm S.D.	Geometrical Mean
k_{-1}^a (h^{-1})	0.18 ± 0.07	0.17
F_1^a	1.41 ± 0.23	1.37
T_{\max}^a (h)	2.30 ± 0.50	2.31 ^c
C_{\max}^a ($\mu\text{g}/\text{ml}$)	7.91 ± 3.38	7.22 ^c
k_{-2}^b (h^{-1})	0.44 ± 0.23	0.38
F_2^b	1.03 ± 0.17	1.02
T_{\max}^b (h)	3.07 ± 0.48	3.06 ^c
C_{\max}^b ($\mu\text{g}/\text{ml}$)	8.60 ± 3.82	7.99 ^c

a) Obtained by using the modified two-compartment model. b) Obtained by using the modified three-compartment model. c) Calculated from the mean concentration-time curve of CTM in pleural effusion.

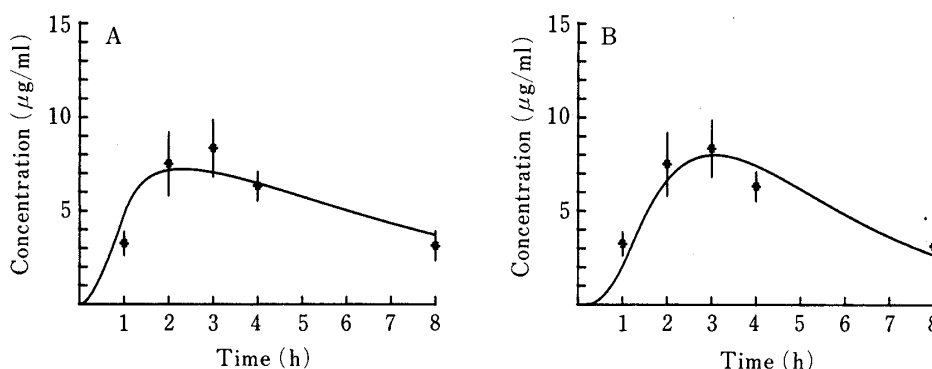


Fig. 3. Concentrations (Mean \pm S.E.) and Mean Concentration-Time Curves of CTM in Pleural Effusion of 6 Patients Following CTM Administration (1 g) by 1 h Constant Rate Intravenous Infusion

A: obtained by using the modified two-compartment model.

B: obtained by using the modified three-compartment model.

squares of differences between the observed concentrations in pleural effusion and the values calculated from Eqs. 8 and 9, respectively. The values of k_{-1} , k_{-2} , F_1 , F_2 , C_{\max} (peak drug concentration) and T_{\max} (time of peak drug concentration) are listed in Table II. The mean concentration-time curves obtained from the geometrical means⁷⁾ of individual V_1 's, α 's, β 's,

k_{21} 's, k_{-1} 's, k_{-2} 's, F_1 's and F_2 's are shown in Fig. 3. Judging from the mean concentration–time curves, it seems more reasonable to use the model in Fig. 2 rather than that in Fig. 1 for the preparation of pharmacokinetic profiles in these examples.

2) Pharmacokinetic Profile of Cefmenoxime (CMX) Concentration in Burn Blister Fluid

The CMX concentration data measured during studies on the transfer of injected CMX to exudates (blisters) at the wounds of burned patients^{4b)} were used for the preparation of pharmacokinetic profiles. Blood samples from 6 patients and burn blister fluid samples from 8 patients, both with normal renal function, were collected at appropriate intervals after bolus intravenous injection of 50 mg/kg of CMX. The serum concentration data were analyzed with the usual two-compartment open model to afford the pharmacokinetic parameters shown in Table III. As the burn blister fluids and blood samples were taken from different patients, CMX concentrations in the burn blister fluids of individual patients were analyzed based on Eq. 4 with the mean serum concentration–time course obtained from the geometrical means of the individual α 's, β 's, k_{21} 's and V_1 's shown in Table III. The values of k_{-1} , F_1 , C_{\max} and

TABLE III. Pharmacokinetic Parameters Obtained from the Serum CMX Levels of Burned Patients ($n=6$)

Parameters	Arithmetic Mean \pm S.D.	Geometrical Mean
α (h^{-1})	5.01 ± 3.03	44.29
β (h^{-1})	0.47 ± 0.09	0.46
$t_{1/2\beta}$ (h)	1.53 ± 0.29	1.51
V_1 (l/kg)	0.155 ± 0.049	0.149
V_d (l/kg)	0.324 ± 0.086	0.315
Cl (ml/min·kg)	2.43 ± 0.22	2.42
AUC ($\mu\text{g}\cdot\text{h}/\text{ml}$)	346 ± 28	345
k_{21} (h^{-1})	2.36 ± 1.52	2.03

TABLE IV. Pharmacokinetic Parameters Obtained from the Concentrations of CMX in Burn Blister Fluid ($n=8$)

Parameters	Arithmetic Mean \pm S.D.	Geometrical Mean
k_{-1} (h^{-1})	0.40 ± 0.12	0.38
F_1	0.43 ± 0.14	0.41
T_{\max} (h)	2.03 ± 0.35	$2.02^a)$
C_{\max} ($\mu\text{g}/\text{ml}$)	23.0 ± 6.61	$22.2^a)$

a) Calculated from the mean concentration–time curve of CMX in burn blister fluid.

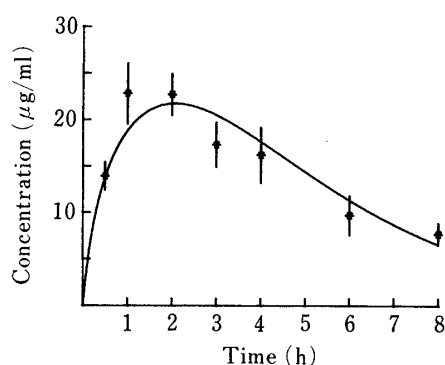


Fig. 4. Concentrations (Mean \pm S.E.) and Mean Concentration–Time Curve of CMX in Burn Blister Fluid of 8 Patients Following Bolus Intravenous Injection of 50 mg/kg CMX.

T_{\max} are listed in Table IV. The mean concentration–time course in burn blister fluids using the geometrical means of individual k_{-1} 's and F_1 's is shown in Fig. 4.

3) Pharmacokinetic Profile of Cefsulodin (CFS) and Cefotiam (CTM) Concentration in Aqueous Humor

The CFS and CTM concentration data reported in studies on the distributions of these drugs to the human aqueous humor and cornea⁶⁾ were used for the preparation of pharmacokinetic profiles. One gram each of CFS or CTM was administered to 37 cataract patients (CFS, 19; CTM, 18) by 30 min intravenous drip infusion prior to ophthalmic operation and aqueous humors were collected from each patient just before the operation.

Since practically only one or two (operation for both eyes) samples were available from one patient, six different intervals between the start of administration and operation, *i.e.*, 1.0, 1.5, 2.0, 2.5, 3.0 or 3.5 h after the start of administration, were adopted, and the combined

TABLE V. Pharmacokinetic Parameters Obtained from the Serum CFS and CTM Levels of Cataract Patients

Parameters	CFS (<i>n</i> =19)		CTM (<i>n</i> =18)	
	Arithmetic Mean \pm S.D.	Geometrical Mean	Arithmetic Mean \pm S.D.	Geometrical Mean
α (h^{-1})	4.05 \pm 2.49	3.41	3.17 \pm 2.41	2.58
β (h^{-1})	0.36 \pm 0.07	0.35	0.52 \pm 0.14	0.50
$t_{1/2\beta}$ (h)	2.02 \pm 0.39	1.98	1.42 \pm 0.33	1.38
V_1 (l)	11.9 \pm 4.9	11.1	9.56 \pm 3.02	9.09
V_d (l)	18.5 \pm 4.0	18.1	13.3 \pm 3.51	12.9
Cl (ml/min)	110 \pm 35	105	114 \pm 42	108
AUC ($\mu\text{g} \cdot \text{h}/\text{ml}$)	163 \pm 40	158	163 \pm 51	155
k_{21} (h^{-1})	2.32 \pm 1.21	2.08	2.02 \pm 1.01	1.82

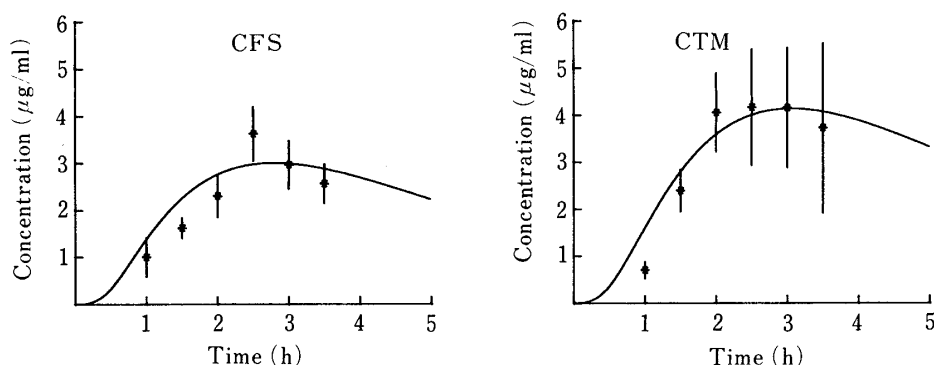


Fig. 5. Concentrations (Mean \pm S.E.) and Concentration–Time Curves of CFS and CTM in Aqueous Humor Following CFS or CTM Administration (1 g) by 30 min Constant Rate Intravenous Infusion

TABLE VI. Pharmacokinetic Parameters Obtained from the Concentrations of CFS and CTM in Aqueous Humor

Parameters	CFS	CTM
k_{-2} (h^{-1})	0.58	0.36
F_2	0.12	0.18
T_{\max} (h)	2.78	3.06
C_{\max} ($\mu\text{g}/\text{ml}$)	3.00	4.14

data from individual patients were used for the analysis. On the other hand, blood samples were collected at 0.5, 1.0, 2.0, 3.0 and 4.0 h after the start of constant rate intravenous infusion from each patient. The serum concentration data were analyzed individually with the usual two-compartment open model (Table V). The mean serum concentration–time courses of CFS and CTM which were computed by using the geometrical means of individual α 's, β 's, k_{21} 's and V_1 's, were substituted individually into Eq. 9, and the optimum values of k_{-2} and F_2 were determined. The values of k_{-2} , F_2 , C_{\max} and T_{\max} for CFS and CTM are listed in Table VI. The CFS and CTM concentration–time curves in the aqueous humor are shown in Fig. 5.

Discussion

Example 1 is a case where the drug concentrations in tissues or fluids were measured along with those in serum for individual patients at appropriate intervals after administration of a drug. Such an example is considered to be virtually an ideal case for the preparation of pharmacokinetic profiles of a drug in tissues or fluids. It is often the case in clinical studies that only the drug concentrations in tissues or fluids are measured and serum drug concentration is unavailable, since exudates such as pleural effusion and blister fluid can be collected more readily than serum. In such a case, one possible approach is to use the mean plasma (or serum) concentration–time course obtained from another group of patients, preferably with the same symptom, or from volunteers. By such a method, a good CMX concentration–time curve in burn blister fluid was obtained in example 2. In this example, a good mean concentration–time curve was obtained by using the modified two-compartment model of Fig. 1. However, in the analysis of the data for individual subjects, there were a few cases where better concentration–time courses were obtained by employing the model of Fig. 2. In the preparation of pharmacokinetic profiles for exudates such as pleural effusion and burn blister fluid, it seems more practical to choose the model according to the degree of inflammation at the affected part. In such a case as example 3, where only one or two samples are obtained from a patient, pharmacokinetic profiles can be conveniently prepared by the combined use of concentration data obtained from different subjects. In this case, at least four or five data for each period of time are required to obtain a reasonable concentration–time curve free from the influence of interindividual difference.

In the two pharmacokinetic models proposed in this paper, the process of a drug transfer is greatly simplified. If the process is treated more strictly, the parameters to be determined will increase and numerous drug concentration–time data will be required in order to obtain reliable pharmacokinetic parameters. However, it is practically impossible to collect many drug concentration–time data for blood, tissues and fluids from one candidate. Nevertheless, it is often the case in clinical studies that determination of pharmacokinetic parameters is desirable when a relatively small number of drug concentration–time data are available. In such a case, the present method, by which drug concentration in tissues and fluids can be analyzed simply using the transfer rate constant (k_{-1} or k_{-2}) and apparent clearance ratio (F_1 or F_2), should be practically useful for the preparation of pharmacokinetic profiles when the plasma (or serum) concentration–time course is available, although the transfer rate constants k_1 and k_2 and apparent volumes of distribution V_2 and V_3 cannot be determined.

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