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A Simple Linear Model for the Simulation of Plasma Concentration–Time Curves Based on the Two-Compartment Open Model[1)]

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A new *in vitro* model has been elaborated for the simulation of plasma concentration curves based on the two-compartment open model. The new method consists of a procedure in which vessels containing water or an aqueous solution of a drug are simply connected in a line and the contents are made to flow at a constant rate from one side to the other. The model is expected to be useful for the study of, for example, the *in vitro* antibacterial activity of antibiotics whose concentrations change according to the two-compartment open model.

Keywords——pharmacokinetics; drug concentration–time curve; *in vitro* model; simulation; two-compartment open model; bolus intravenous injection; constant rate intravenous infusion; first-order absorption

In vitro models to simulate drug concentration–time curves in plasma or serum based on the one-compartment open model were described by Rowe and Morozowich.[2)] More recently, analog experimental systems for the simulation of plasma concentration curves based on the one- and two-compartment open models were developed by Takada[3)] and Goto.[4)] These systems are convenient not only for the simulation of drug concentrations but also for improving our understanding of the principles of pharmacokinetics. In the field of chemotherapy, for instance, analog experimental systems have been used for studying the *in vitro* antibacterial activity of antibiotics whose concentrations change with time, as is usually the case in plasma, fluids and tissues after *in vivo* administration.[5,6)] However, those systems representing the two-compartment open model require a rather complex procedure to circulate a solution between two vessels corresponding to the first (central) and second (peripheral) compartment.

In this paper we wish to propose a new model to simulate plasma concentration curves which does not involve circulation of solution between two vessels. By using this new model, plasma concentration curves based on the two-compartment open model can be obtained simply from the concentration in the last vessel, similarly to the case of the known one-compartment open model. The present method consists of a procedure in which vessels containing a certain amount of water or an aqueous solution with an appropriate concentration of a drug are connected in a line and the contents are made to flow at a constant rate from one side to the other side of the linearly coupled vessels.

Results

a) Bolus Intravenous Injection

The two-compartment open model with first-order absorption is schematically shown in Fig. 1. The scheme indicates that a drug incorporated into the first compartment is eliminated with a rate constant of r, while a part of the drug is transferred to the second compartment and returned to the first compartment with rate constants of p and q, respectively.

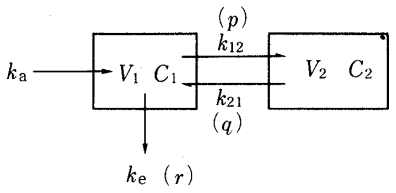

Fig. 1. Schematic Diagram of the Two-Compartment Open Model

V_1: apparent volume of distribution in central compartment.
V_2: apparent volume of distribution in peripheral compartment.
C_1: drug concentration in central compartment.
C_2: drug concentration in peripheral compartment.
k_a: absorption rate constant.
$k_e(r)$: elimination rate constant.
$k_{12}(p)$, $k_{21}(q)$: transfer rate constant.

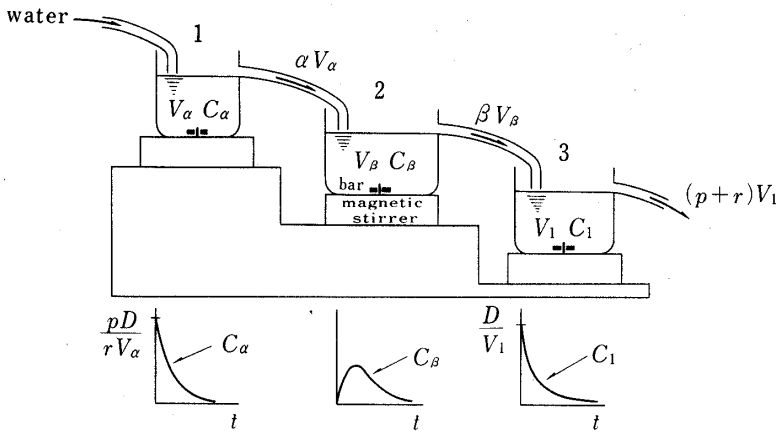

Fig. 2. Schematic *in Vitro* Model to Simulate Drug Concentration–Time Curves in Plasma or Serum Based on the Two-Compartment Open Model with Bolus Intravenous Injection

In this model, the flow rate is given by $(p+r)V_1=\alpha V_\alpha=\beta V_\beta$.

In an effort to obtain the same situation with a simple linear model, a new *in vitro* system for the two-compartment open model with bolus intravenous injection has been designed. This system consists of three vessels linearly connected on platforms at different levels, as illustrated in Fig. 2.

In the scheme of Fig. 1, when an amount D of a drug is administered to the first compartment, it will be apparently eliminated from there with a rate constant of $p+r$, while pD/r of the drug will pass through the second compartment and return to the first compartment. This situation can be realized in the scheme of Fig. 2 when V_1 of water containing D of a drug, $(p+r)V_1/\beta\,(=V_\beta)$ of water, and $(p+r)V_1/\alpha\,(=V_\alpha)$ of aqueous solution containing pD/r of the drug are placed in vessels 3, 2 and 1, respectively, and water is made to flow into vessel 1 with a flow rate of $(p+r)V_1$. The flow rate between vessels 1 and 2, and between vessels 2 and 3, which are equal to $(p+r)V_1$, are expressed by αV_α and βV_β, respectively. The elimination rate of the drug in vessel 1 is expressed by the differential equation (1), where dQ/dt, C_α, and $\alpha V_\alpha C_\alpha \Delta t$ are the elimination rate, the drug concentration in vessel 1, and the amount of the drug eliminated from vessel 1 during Δt, respectively. Integration of Eq. (1) leads to Eq. (2), which represents the drug concentration in vessel 1 as a

$$\left.\begin{aligned} \frac{dQ}{dt} &= \lim_{\Delta t\to 0}\frac{-\alpha V_\alpha C_\alpha \Delta t}{\Delta t} = -\alpha V_\alpha C_\alpha \\ \frac{dC_\alpha}{dt} &= -\alpha C_\alpha \end{aligned}\right\} \quad (1)$$

$$C_\alpha = \frac{pD}{rV_\alpha}e^{-\alpha t} \quad (2)$$

function of time. The rate of change of the drug concentration in vessel 2 is given by the differential equation (3a), since $\alpha V_\alpha C_\alpha \Delta t$ of the drug enters the vessel and $\beta V_\beta C_\beta \Delta t$ flows out

during Δt. Equation (3b) is obtained by applying the relationship $\alpha V_\alpha = \beta V_\beta$ and substituting Eq. (2) for C_α into Eq. (3a). Integration of Eq. (3b) leads to Eq. (4), which represents the drug

$$\frac{dC_\beta}{dt} = \lim_{\Delta t \to 0} \frac{\alpha V_\alpha C_\alpha \Delta t - \beta V_\beta C_\beta \Delta t}{V_\beta \Delta t} \tag{3a}$$

$$\frac{dC_\beta}{dt} = \beta \left(\frac{pD}{rV_\alpha} e^{-\alpha t} - C_\beta \right) \tag{3b}$$

$$C_\beta = \frac{pD}{rV_\beta} \frac{\alpha}{\alpha - \beta} (e^{-\beta t} - e^{-\alpha t}) \tag{4}$$

concentration in vessel 2. The drug concentration–time curves given by Eqs. (2) and (4) are very similar to those in plasma based on the one-compartment open model with bolus intravenous injection and with first-order absorption, respectively. Furthermore, Eq. (4) represents the drug concentration in the second compartment when V_2 is equal to $(p+r)V_1/q$. The rate of change of the drug concentration in vessel 3 is expressed by the differential equation (5). Integration of Eq. (5) leads to Eq. (6), taking into account the initial

$$\frac{dC_1}{dt} = \lim_{\Delta t \to 0} \frac{\beta V_\beta C_\beta \Delta t - (p+r) V_1 C_1 \Delta t}{V_1 \Delta t} = \frac{\alpha\beta pD}{(\alpha - \beta) r V_1} (e^{-\beta t} - e^{-\alpha t}) - (p+r) C_1 \tag{5}$$

$$C_1 = \frac{\alpha\beta pD}{(\alpha - \beta) r V_1} \left\{ \frac{e^{-\alpha t}}{\alpha - (p+r)} + \frac{e^{-\beta t}}{(p+r) - \beta} \right\} + f e^{-(p+r)t} \tag{6}$$

$$f = \left\{ 1 - \frac{\alpha\beta p}{r(\alpha - p - r)(p + r - \beta)} \right\} \frac{D}{V_1}$$

concentration (D/V_1) in vessel 3 at zero time. For the two-compartment open model shown in Fig. 1, Eq. (7) gives the relationship between the transfer and elimination rate constants p, q and r, and the hybrid rate constants α and β. Substitution of the relationship in Eq. (7) into Eq. (6) leads to Eq. (8), which is a well-known equation for the two-compartment open model with bolus intravenous injection. In the model of Fig. 2, the drug concentration in vessel 3 is also given by Eq. (8), when V_β of aqueous solution containing pD/r of drug and V_α of water are placed in vessels 1 and 2, respectively.

$$\left.\begin{aligned} \alpha + \beta &= p + q + r \\ \alpha\beta &= qr \end{aligned}\right\} \tag{7}$$

$$C_1 = A_1 e^{-\alpha t} + B_1 e^{-\beta t} \tag{8}$$

$$A_1 = \frac{\alpha - q}{\alpha - \beta} \frac{D}{V_1}, \qquad B_1 = \frac{q - \beta}{\alpha - \beta} \frac{D}{V_1}$$

b) Constant Rate Intravenous Infusion

In the case of intravenous infusion, two types of model as shown in Figs. 3 and 4 can be set up.

The model of Fig. 3 depends on essentially the same concept as the schematic diagram in Fig. 2. In the case that a drug is infused into the first (central) compartment at a constant rate K during t_0, the amount of the drug passing through the second (peripheral) compartment can be expressed by pKt_0/r. Therefore, in the model of Fig. 3, vessel 3 has been designed so as to reflect the situation that Kt_0 of the drug is directly infused into the vessel during t_0 while pKt_0/r of the drug is infused into the vessel through vessel 2, which corresponds to the second compartment. Thus, V_α and V_β of aqueous solution with a drug concentration of $K/(p+r)V_1$ are placed in vessels 1 and 2, respectively, and V_1 of water is put in vessel 3. When an aqueous solution with a drug concentration of K/rV_1 is made to flow into vessel 1 at a constant rate of

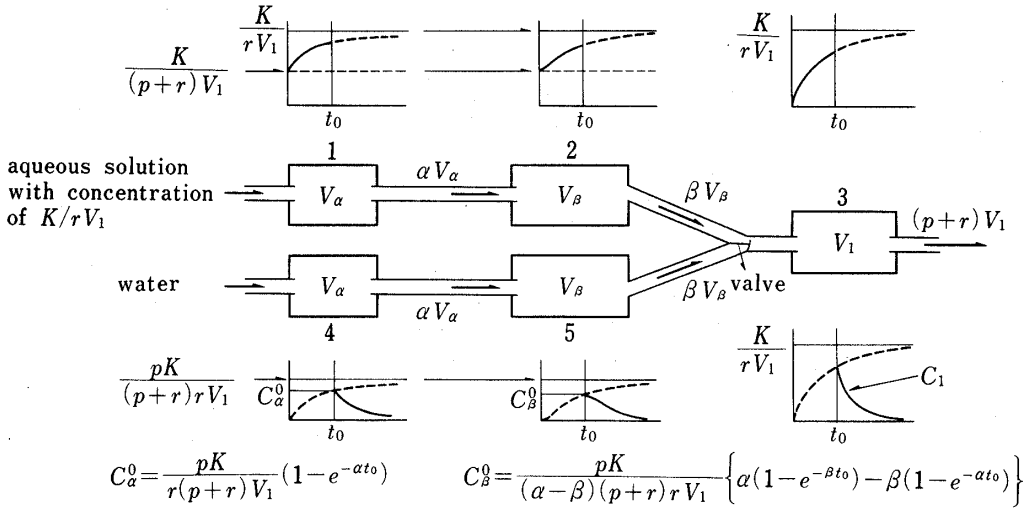

Fig. 3. Schematic Diagram of the *in Vitro* Model to Simulate Drug Concentration–Time Curves in Plasma or Serum Based on the Two-Compartment Open Model with Constant Rate Intravenous Infusion

The flow rate is given by $(p+r)V_1=\alpha V_\alpha=\beta V_\beta$. C_α^0 and C_β^0 are the initial concentrations in vessels 4 and 5, respectively.

$(p+r)V_1$, the change of the drug concentration in each vessel is shown by the concentration–time curve depicted above each vessel in Fig. 3. The rate of change of the drug concentration in vessels 1, 2 and 3 is given by the differential equations (9), (11) and (13), respectively. By solving these equations taking into account the initial concentration in each vessel, Eqs. (10), (12) and (14) are obtained. The underlined term in Eq. (12) represents the drug concentration

$$\frac{dD_\alpha}{dt}=\lim_{\Delta t\to 0}\frac{\frac{K}{rV_1}(p+r)V_1\Delta t-\alpha V_\alpha C_\alpha\Delta t}{V_\alpha\Delta t}=\frac{(p+r)K}{rV_\alpha}-\alpha C_\alpha \tag{9}$$

$$C_\alpha=\frac{K}{(p+r)V_1}+\frac{pK}{(p+r)rV_1}(1-e^{-\alpha t}) \tag{10}$$

$$\frac{dC_\beta}{dt}=\lim_{\Delta t\to 0}\frac{\alpha V_\alpha C_\alpha\Delta t-\beta V_\beta C_\beta\Delta t}{V_\beta\Delta t}=\beta(C_\alpha-C_\beta) \tag{11}$$

$$C_\beta=\frac{K}{(p+r)V_1}+\underline{\frac{pK}{(\alpha-\beta)(p+r)rV_1}\{\alpha(1-e^{-\beta t})-\beta(1-e^{-\alpha t})\}} \tag{12}$$

$$\frac{dC_1}{dt}=\lim_{\Delta t\to 0}\frac{\beta V_\beta C_\beta\Delta t-(p+r)V_1C_1\Delta t}{V_1\Delta t}=(p+r)(C_\beta-C_1) \tag{13}$$

$$C_1=\frac{K}{rV_1}-\frac{pK}{(\alpha-\beta)rV_1}\left\{\frac{\beta e^{-\alpha t}}{\alpha-(p+r)}+\frac{\alpha e^{-\beta t}}{(p+r)-\beta}\right\}+fe^{-(p+r)t} \tag{14}$$

$$f=\frac{K}{rV_1}\left\{\frac{p(\alpha+\beta-p-r)}{(\alpha-p-r)(p+r-\beta)}-1\right\}$$

in the second compartment when V_2 is equal to $(p+r)V_1/q$. Substitution of the relationship in Eq. (7) into Eq. (14) leads to Eq. (15a), a well-known equation for infusion based on the two-compartment open model. The model in Fig. 3 works as follows. Initially, V_α and V_β of aqueous solution at the concentrations shown below each vessel are placed in vessels 4 and 5, respectively. These concentrations are obtained by subtracting $K/(p+r)V_1$ from the con-

centrations of vessels 1 and 2 at the end of infusion. At the end of infusion, water is made to flow into vessel 4 at the same flow rate as that during the infusion. Then the drug concentration–time curves in vessels 4, 5 and 3 will be as shown below each vessel in Fig. 3. The drug concentrations in vessels 4, 5 and 3 are given by Eqs. (16), (17) and (18), respectively. In these equations, t_0 is the infusion time and t' represents the time since the end of infusion, that is, $t-t_0$. The factor f in Eq. (18) is identical with that in Eq. (14). Substitution of the relationship in Eq. (7) into Eq. (18) leads to Eq. (15b), corresponding to the well-known equation for infusion.

$$C_1=A_1^*(1-e^{-\alpha t})+B^*(1-e^{-\beta t}) \tag{15a}$$

$$A_1^*=\frac{\alpha-q}{\alpha-\beta}\frac{K}{\alpha V_1}, \qquad B_1^*=\frac{q-\beta}{\alpha-\beta}\frac{K}{\beta V_1}$$

$$C_1=A_1e^{-\alpha t'}+B_1e^{-\beta t'} \tag{15b}$$

$$A_1=(1-e^{-\alpha t_0})A_1^*, \qquad B_1=(1-e^{-\beta t_0})B_1^*$$

$$C_\alpha=\frac{pK}{(p+r)rV_1}(1-e^{-\alpha t_0})e^{-\alpha t'} \tag{16}$$

$$C_\beta=\frac{pK}{(\alpha-\beta)(p+r)rV_1}\{\alpha(1-e^{-\beta t_0})e^{-\beta t'}-\beta(1-e^{-\alpha t_0})e^{-\alpha t'}\} \tag{17}$$

$$C_1=\frac{\beta pK(1-e^{-\alpha t_0})}{(\alpha-\beta)(\alpha-p-r)rV_1}e^{-\alpha t'}+\frac{\alpha pK(1-e^{-\beta t_0})}{(\alpha-\beta)(p+r-\beta)rV_1}e^{-\beta t'} \tag{18}$$
$$-f(1-e^{-(p+r)t_0})e^{-(p+r)t'}$$

An alternative *in vitro* method to represent the two-compartment model was also designed and is illustrated in Fig. 4. In the two-compartment open model, the drug concentration in the first compartment during infusion reaches a steady state more slowly than in the case of the one-compartment model owing to the partial transfer to the second compartment. The concentration–time curve represented by Eq. (15a) is realized in vessel 3 of Fig. 4 by subtracting pK/qr, which corresponds to the amount of drug in the second

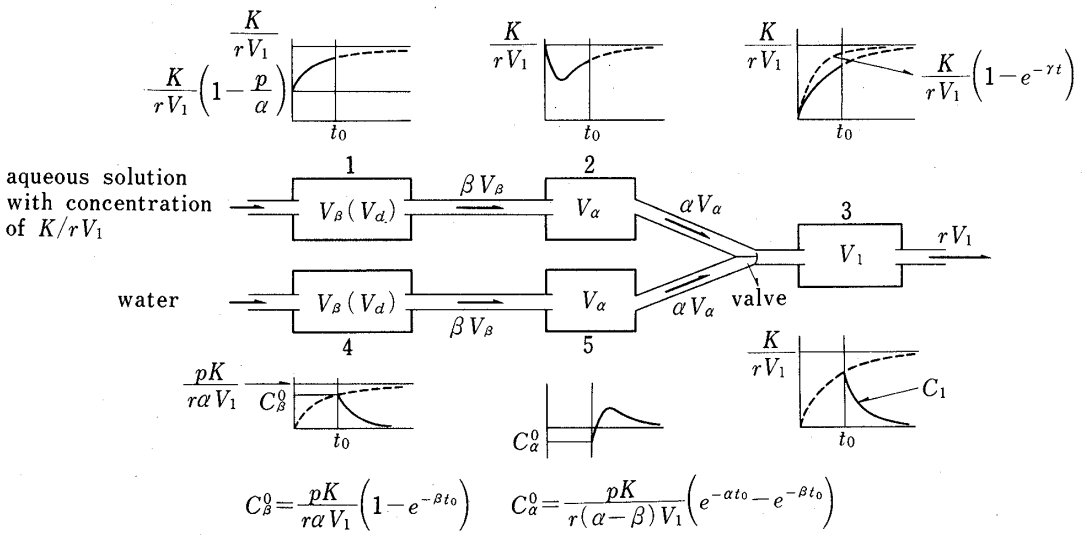

Fig. 4. Schematic Diagram of the *in Vitro* Model to Simulate Drug Concentration–Time Curves in Plasma or Serum Based on the Two-Compartment Open Model with Constant Rate Intravenous Infusion

The flow rate is given by $rV_1=\alpha V_\alpha=\beta V_\beta$. C_β^0 and C_α^0 are the initial concentration in vessels 4 and 5, respectively.

compartment in the steady state, from the amount of drug contained in vessel 1, while an aqueous solution with a concentration of K/rV_1 is made to flow into vessel 1. That is, V_β $(=V_d)$ of aqueous solution containing $KV_\beta/rV_1-pK/qr$ of drug, V_α $(=rV_1/\alpha)$ of aqueous solution with a concentration of K/rV_1 and V_1 of water are placed in vessels 1, 2 and 3, respectively. When an aqueous solution with a concentration of K/rV_1 is made to flow into vessel 1 at a constant rate of rV_1, the drug concentration–time curves in vessels 1, 2 and 3 are represented by the diagrams shown above each vessel in Fig. 4. The drug concentrations in the vessels are given by Eqs. (19), (20) and (21), respectively. Substitution of the relationship in Eq. (7) into Eq. (21) leads to Eq. (15a). At the end of infusion, the amount of the drug

$$C_\beta=\frac{K}{rV_1}\left(1-\frac{p}{\alpha}e^{-\beta t}\right) \tag{19}$$

$$C_\alpha=\frac{K}{rV_1}\left\{1-\frac{p}{\alpha-\beta}(e^{-\beta t}-e^{-\alpha t})\right\} \tag{20}$$

$$C_1=\frac{K}{rV_1}-\frac{pK}{(\alpha-\beta)V_1}\left(\frac{e^{-\alpha t}}{\alpha-r}+\frac{e^{-\beta t}}{r-\beta}\right)+fe^{-rt} \tag{21}$$

$$f=\frac{K}{rV_1}\left\{\frac{pr}{(\alpha-r)(r-\beta)}-1\right\}$$

subtracted from vessel 1 during infusion has to be compensated for. The amount of drug sent to vessel 2 from vessel 1 during an infusion period of t_0 is less by the amount of $pK(1-e^{-\beta t_0})/\alpha\beta$ than in the case that an aqueous solution with a concentration of K/rV_1 is put into vessel 1. Therefore V_β of aqueous solution containing $pK(1-e^{-\beta t_0})/\alpha\beta$ of drug is placed in vessel 4. Next V_α of aqueous solution with the concentration obtained by subtracting the concentration in the steady state from that at the end of infusion is placed in vessel 5. The product of the elimination rate constant r and the difference in concentration between the solutions in vessels 3 and 5 is equal to the slope of the concentration in vessel 3 immediately after the end of infusion. That is, V_β and V_α of aqueous solutions with the concentrations C_β^0 and C_α^0 shown in Fig. 4 are previously placed in vessels 4 and 5, respectively. When water at a flow rate of rV_1 is passed into vessel 4, the drug concentration–time curves in vessels 4, 5 and 3 are as shown below each vessel in Fig. 4. The drug concentrations in vessels 4, 5 and 3 are given by Eqs. (22), (23) and (24), respectively. The factor f in Eq. (24) is identical with that in

$$C_\beta=\frac{pK}{r\alpha V_1}(1-e^{-\beta t_0})e^{-\beta t'} \tag{22}$$

$$C_\alpha=\frac{pK}{r(\alpha-\beta)V_1}\{(1-e^{-\beta t_0})e^{-\beta t'}-(1-e^{-\alpha t_0})e^{-\alpha t'}\} \tag{23}$$

$$C_1=\frac{pK(1-e^{-\alpha t_0})}{(\alpha-\beta)(\alpha-r)V_1}e^{-\alpha t'}+\frac{pK(1-e^{-\beta t_0})}{(\alpha-\beta)(r-\beta)V_1}e^{-\beta t'}-f(1-e^{-rt_0})e^{-rt'} \tag{24}$$

Eq. 21. Substitution of the relationship in Eq. (7) into Eq. (24) leads to Eq. (15b). It should be noted, however, that this model is only applicable when the time of infusion (t_0) is long enough for the drug concentration in the first compartment to reach a steady state. As can be seen in Fig. 4, a negative value of C_α^0 in vessel 5 is obtained when t_0 is too small.

c) Administration with First-Order Absorption

In the case of first-order absorption, a model as illustrated in Fig. 5 is set up. This model is similar to that in Fig. 2 except that a new vessel is placed between vessels 2 and 3 in Fig. 2. In this case, the administered drug is passed to the first compartment by two routes, *i.e.*, directly from the administration (absorption) site and by way of the second compartment. Vessel 3 in

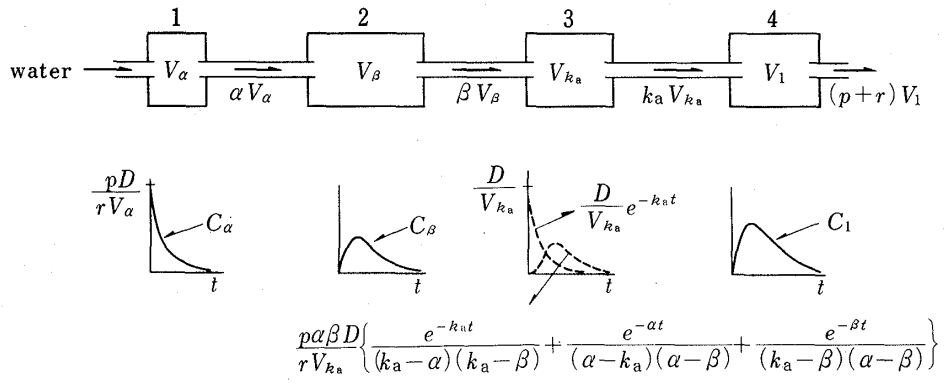

Fig. 5. Schematic Diagram of the *in Vitro* Model to Simulate Drug Concentration–Time Curves in Plasma or Serum Based on the Two-Compartment Open Model with First-Order Absorption

The flow rate is given by $(p+r)V_1=\alpha V_\alpha=\beta V_\beta=k_a V_{k_a}$.

Fig. 5 involves these two functions. Thus, the drug in the absorption site is prepared by dissolving the drug in vessel 3 and the drug from the second compartment is sent from vessel 1 through vessel 2. Accordingly, a volume V_α of aqueous solution containing pD/r of a drug (which corresponds to the amount passing through the second compartment), V_β of water, $(p+r)V_1/k_a\ (=V_{k_a})$ of aqueous solution containing D of the drug and V_1 of water are placed in vessels 1, 2, 3 and 4, respectively. When water is made to flow at a constant rate of $(p+r)V_1$ into vessel 1, the drug concentrations in vessels 1 and 2 are given by Eqs. (2) and (4), respectively. In vessel 3, the drug concentration is given by Eq. (25). This equation consists of

$$C_{k_a}=\frac{p\alpha\beta D}{rV_{k_a}}\left\{\frac{e^{-k_a t}}{(k_a-\alpha)(k_a-\beta)}+\frac{e^{-\alpha t}}{(\alpha-k_a)(\alpha-\beta)}+\frac{e^{-\beta t}}{(k_a-\beta)(\alpha-\beta)}\right\}+\frac{D}{V_{k_a}}e^{-k_a t} \tag{25}$$

$$C_1=\frac{k_a D}{V_1}\left\{\frac{(q-k_a)e^{-k_a t}}{(k_a-\alpha)(k_a-\beta)}+\frac{(\alpha-q)e^{-\alpha t}}{(k_a-\alpha)(\alpha-\beta)}+\frac{(q-\beta)e^{-\beta t}}{(k_a-\beta)(\alpha-\beta)}\right\} \tag{26}$$

two terms corresponding to the drug concentration passed to vessel 3 from vessel 2 and the drug previously dissolved in vessel 3. The first term in Eq. (25) is consistent with the equation for the drug concentration in the second compartment when V_2 is equal to $(p+r)V_1/q$. The second term in that equation corresponds to the drug concentration at the absorption site. The drug concentration in vessel 4 is given by Eq. (26) when the relationship shown in Eq. (7) is maintained. Equation (26) is identical with the equation representing the drug concentration in plasma based on the two-compartment open model with first-order absorption.

Discussion

In the systems proposed in this paper, the hybrid rate constants α and β, estimated directly from the results of analysis of drug concentration data in plasma, can be used for the preparation of the drug concentration–time curves, although the transfer rate constants p and q, and the elimination rate constant r are also used for the determination of V_α, V_β and the initial concentrations in the vessels. Conventional analog experimental systems might be superior to the present linear systems in terms of understanding the mechanism of the changes of drug concentration in plasma. However, the *in vitro* antibacterial activity of antibiotics can be studied more easily in the present linear systems which are based on a simple concept similar to that of the one-compartment open model, since no circulating steps between the two vessels are necessary and therefore the circulation of bacteria between the two vessels need not

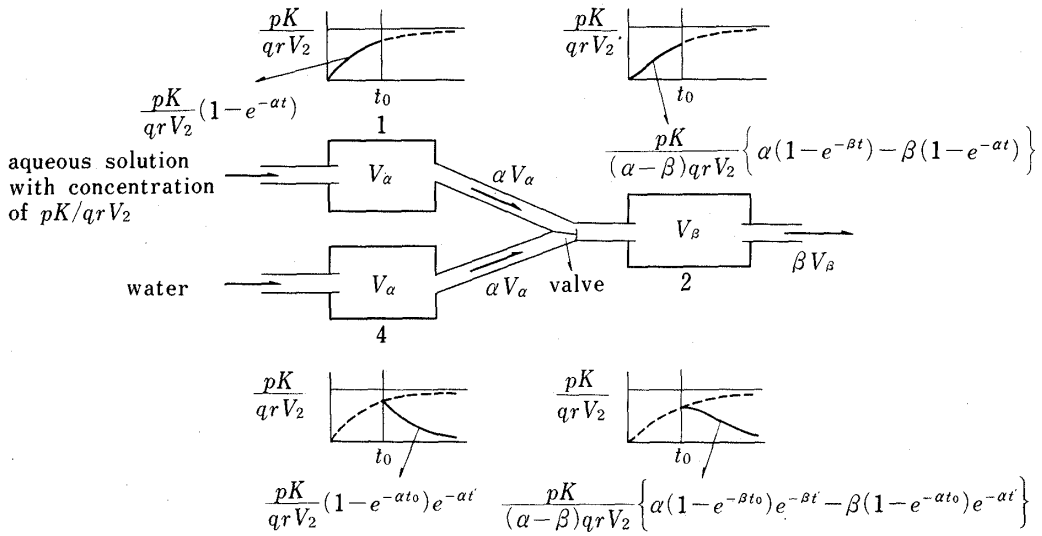

Fig. 6. Schematic Diagram of the *in Vitro* Model to Simulate Drug Concentration–Time Curves in the Second Compartment Based on the Two-Compartment Open Model with Constant Rate Intravenous Infusion

In this model, both $(p+r)V_1$ and rV_1 can be used as flow rates. When the former is used, V_α and V_β are equal to $(p+r)V_1/\alpha$ and $(p+r)V_1/\beta$, respectively. In case of the latter, V_α and V_β are equal to rV_1/α and rV_1/β, respectively.

be taken into account in a study of the time-course of antibiotic activity.

Moreover, the present systems shown in Figs. 2, 3 and 5 are particularly useful for the simulation of drug concentration–time curves in the second compartment, which corresponds to, for example, fluids and tissues. Thus, in the case of bolus intravenous injection, the drug concentration in vessel 2 will be identical with that in the second compartment when the initial concentration in vessel 1 in Fig. 2 is set at $pD/\beta V_2$ instead of pD/rV_α. In the system with constant rate intravenous infusion shown in Fig. 3, drug concentration–time curves in the second compartment during and after the infusion can be produced in vessels 2 and 5, respectively. In this case, the system of Fig. 3 can be simplified into that of Fig. 6, where the drug concentration–time curve in the second compartment during infusion is obtained in vessel 2 by setting the initial concentrations in both vessels 1 and 2 to zero and passing an aqueous solution with a concentration of pK/qrV_2 into vessel 1. At the end of infusion, the initial concentration in vessel 4 is set at $pK(1-e^{-\alpha t_0})/qrV_2$ and water is made to flow into vessel 4 at the same rate as that during the infusion. Then the drug concentration in vessel 2 will correspond to that in the second compartment after infusion.

On the other hand, in the case of the system for first-order absorption in Fig. 5, the drug concentration–time curve in the second compartment is obtained in vessel 3 when the initial concentrations in vessels 2 and 3 are set to $pD/\beta V_2$ and zero instead of pD/rV_α and D/V_{k_a}, respectively.

Thus the new *in vitro* models proposed in this paper are expected to be useful for the simulation of drug concentration–time curves in plasma, fluids and tissues, and should be applicable to such studies as the analysis of the *in vitro* antibacterial activity of antibiotics whose concentrations change according to the two-compartment open model.

Method

Experimental equipment for the two-compartment open model with bolus intravenous injection is shown in Fig. 7. The apparatus consists mainly of three Erlenmeyer flask, 1 (200 ml), 2 (500 ml) and 3 (200 ml) which correspond to vessels 1, 2 and 3 in Fig. 2, respectively. The flasks 1, 2 and 3 are fitted with two-hole or three-hole rubber stoppers

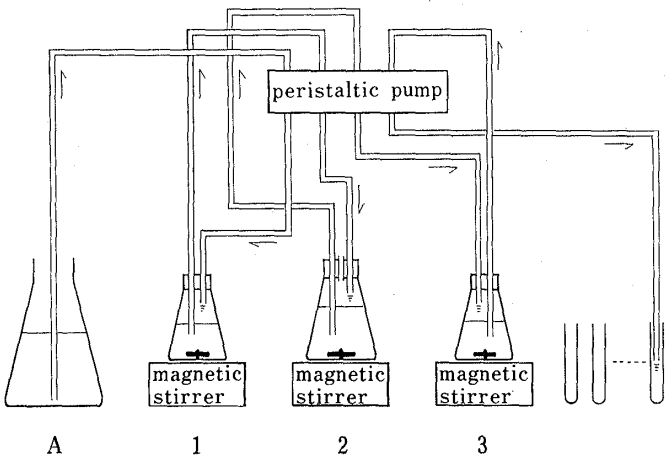

Fig. 7. Experimental Equipment for the Two-Compartment Open Model with Bolus Intravenous Injection

One of the three holes in the stopper of flask 2 was used for sampling.

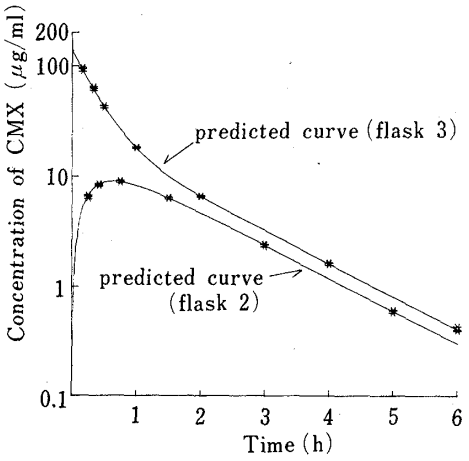

Fig. 8. Reproducibility of CMX Concentrations in the Simple Linear Model Simulating Human Serum Concentrations after an Intravenous Injection of 1 g

*: observed values ($n=3$).

and connected with silicon tubing as shown in Fig. 7. Flasks 1 and 3 are also connected to an Erlenmeyer flask A (3000 ml) containing distilled water and a test tube to collect the solution flowing from flask 3, respectively. The solutions in each flask are pumped at a flow rate of 5 ml/min by a Yamato PA-41A peristaltic pump. With this simple linear model, simulation of the concentrations of cefmenoxime (CMX, Takeda Chemical) in human serum after an intravenous injection of 1 g was verified, and the accuracy and reproducibility of the drug concentrations were studied. The values of α, β, p, q, r and V_1 were computed from analyses of serum concentration data of 50 human subjects with normal renal functions as 3.00, 0.68, 0.72, 1.09, 1.87 h^{-1} and 7.25 l, respectively.[7] In this case, the values of $(p+r)V_1$, V_α, V_β and pD/r were calculated as 313 ml/min, 6.26 l, 27.6 l and 385 mg, respectively. As the pump flow rate used in this experiment was 5 ml/min, the volumes of solutions in flasks 1, 2 and 3, and the amounts of drug dissolved in flasks 1 and 3 could be determined by multiplying V_α, V_β, V_1, pD/r and D by 5/313, respectively. Thus, 100 ml of water containing 6.15 mg of CMX, 441 ml of distilled water, 116 ml of water containing 16.0 mg of CMX and more than 1800 ml (5 ml/min × 360 min) of water were placed in flasks 1, 2, 3 and A, respectively, and magnetic stirrers ensured homogeneous mixing in flasks 1, 2 and 3. The pump was started, and flask 3 was sampled at 10, 20, 30, 60, 120, 240 and 360 min by collecting 0.5 ml portions of solution flowing from the flask. At the same time, 0.5 ml of solution was also taken directly from flask 2 at 15, 25, 45, 90, 180 and 300 min; 0.5 ml of distilled water was added to the flask immediately after each sampling. The concentrations of CMX were determined by using a Nagel Nucleosil $5C_{18}$ (150 × 4 mm) column and a Waters high performance liquid chromatography system consisting of a 6000A solvent delivery unit, a 440 ultraviolet spectrophotometer (set at 254 nm) and a U6K injector. A mixture of H_2O–CH_3CN–CH_3COOH (40 : 20 : 1) was used as the eluent at a flow rate of 0.7 ml/min. The predicted concentration–time curves and observed concentrations of CMX in flasks 2 and 3 were plotted by a Hewlett Packard 7225B plotter (Fig. 8). The observed values in flask 2 as well as flask 3 agreed very closely with the predicted concentration–time curves. Thus, it was proved that the simulated concentrations of CMX in flask 3 of the simple linear model accurately reproduced the serum concentrations of CMX in human subjects.

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References and Notes

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7) The values of α, β, q, r and V_1 were calculated from the individual values for 50 human subjects by the geometrical mean method, and the value of p was determined from Eq. (7).