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A Method for the Pharmacokinetic Analysis of Serum Cefotiam Levels during Cardiopulmonary Bypass Surgery

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In our previous study on serum concentrations of CTM during open-heart operations, it was found in several cases that the serum concentrations after the institution of the cardiopulmonary bypass (CPB) showed an initial transient rise and subsequent slow decline. However, the mechanism of the phenomenon has not been clarified pharmacokinetically. In this paper, a method is proposed by which the serum concentration during CPB can be analyzed simply by using the volume of priming solution (V_p) and rate of decrease (μ) of transfer (k_{12}) and elimination (k_e) rate constants when the pharmacokinetic parameters before or after CPB are available. By using this method, the serum concentrations of patients undergoing open-heart operation were successfully analyzed.

Keywords—pharmacokinetic analysis; open-heart operation; cardiopulmonary bypass (CPB); priming solution; apparent rate constant; pharmacokinetic profile during CPB; two-compartment open model; cefotiam

Cephalosporin antibiotics have been widely used during cardiac surgery to prevent operative and postoperative infection. In this regard, studies aimed at ensuring efficient use of prophylactic antibiotics for patients undergoing open-heart operation were reported by several groups.^{1,2)} Two of the present authors (K.W. and S.S.) and their coworkers attempted to establish an adequate regimen of cefotiam (CTM) prophylaxis for open-heart operation by measuring CTM concentrations in serum and urine mainly during cardiopulmonary bypass (CPB).³⁾ At this time, it was found in several cases that the serum concentration after the institution of CPB showed an initial brief rise and then declined slowly. Such a phenomenon has also been reported in studies on other cephalosporins.²⁾ However, the mechanism of the phenomenon has not been studied pharmacokinetically.

In the present paper we wish to report a method by which serum concentrations during CPB can be successfully analyzed with the two-compartment open model.

Method

When the elimination and distribution of drugs administered intravenously follow linear pharmacokinetics under the experimental conditions, serum (or plasma) concentration-time courses can usually be analyzed with the two-compartment open model shown in Fig. 1-a. After the institution of CPB, it can be predicted that the pharmacokinetic parameters in Fig. 1-a change as shown in Fig. 1-b. That is, the drug concentration in the central compartment is diluted from C_1 to $C_1 V_1 / (V_1 + V_p)$, since the distribution volume of the central compartment increases by V_p due to the CPB priming solution.⁴⁾ The rate constants of elimination (k_e) and transfer (k_{12}) from the central to the peripheral compartment apparently decrease as a result of the dilution. The rate of decrease (μ) of the apparent rate constants is affected by the rate of dilution and the change of renal blood flow and organ perfusion. The serum concentration-time course during CPB will be determined by the rate of dilution and μ on the assumption that

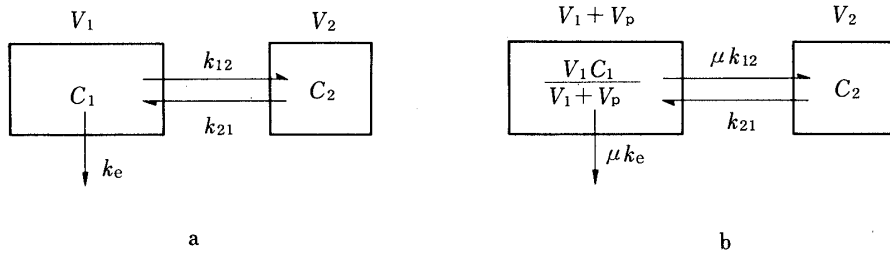


Fig. 1. Schematic Diagram of the Two-Compartment Open Model

a, usual type; b, during CPB.
 V_1, V_2 : apparent volume of distribution in central and peripheral compartment.
 V_p : volume of priming solution.
 C_1, C_2 : drug concentration in central and peripheral compartment.
 k_e : elimination rate constant.
 k_{12}, k_{21} : transfer rate constant.
 μ : rate of decrease of k_e and k_{12} .

the transfer rate constant (k_{21}) from the peripheral to the central compartment does not change, if the values of V_1, k_{12}, k_{21} and k_e are available.

On the other hand, drug concentrations in the central and peripheral compartments after bolus intravenous injection are given by the well-known Eqs. 1 and 2, respectively, where α and β are the hybrid rate constants. If the amount of the drug (Q_1) in the central compartment and that (Q_2) in the peripheral compartment are both zero just before the administration, Q_1 is equal to the dose (D) and Q_2 is zero just after the administration.

$$C_1 = A_1 e^{-\alpha t} + B_1 e^{-\beta t} \tag{1}$$

$$A_1 = \frac{(\alpha - k_{21})Q_1 - k_{21}Q_2}{(\alpha - \beta)V_1}, \quad B_1 = \frac{(k_{21} - \beta)Q_1 + k_{21}Q_2}{(\alpha - \beta)V_1}$$

$$C_2 = A_2 e^{-\alpha t} + B_2 e^{-\beta t} \tag{2}$$

$$A_2 = \frac{-k_{12}V_1A_1}{(\alpha - k_{21})V_2} = \frac{-k_{12}Q_1 + (k_{21} - \beta)Q_2}{(\alpha - \beta)V_2}$$

$$B_2 = \frac{k_{12}V_1B_1}{(k_{21} - \beta)V_2} = \frac{k_{12}Q_1 + (\alpha - k_{21})Q_2}{(\alpha - \beta)V_2}$$

During CPB, the serum concentration–time course is expressed by Eq. 3. In Eq. 3, t_s represents the time at the start of CPB. The hybrid rate constants α' and β' are calculated from Eqs. 4a and 4b, respectively, by using $\mu k_{12}, k_{21}$ and μk_e shown in Fig. 1-b. The amounts of the drug in the central and peripheral compartments at $t = t_s$ are evaluated from Eqs. 5a and 5b, respectively.

$$C_1 = A_1 e^{-\alpha'(t-t_s)} + B_1 e^{-\beta'(t-t_s)} \tag{3}$$

$$A_1 = \frac{(\alpha' - k_{21})Q_1(t_s) - k_{21}Q_2(t_s)}{(\alpha' - \beta')(V_1 + V_p)}$$

$$B_1 = \frac{(k_{21} - \beta')Q_1(t_s) + k_{21}Q_2(t_s)}{(\alpha' - \beta')(V_1 + V_p)}$$

$$\alpha' = \{ \mu k_{12} + k_{21} + \mu k_e + \sqrt{(\mu k_{12} + k_{21} + \mu k_e)^2 - 4\mu k_{21}k_e} \} / 2 \tag{4a}$$

$$\beta' = \{ \mu k_{12} + k_{21} + \mu k_e - \sqrt{(\mu k_{12} + k_{21} + \mu k_e)^2 - 4\mu k_{21}k_e} \} / 2 \tag{4b}$$

$$Q_1(t_s) = A_1 V_1 e^{-\alpha t_s} + B_1 V_1 e^{-\beta t_s} \tag{5a}$$

$$A_1 V_1 = \frac{(\alpha - k_{21})D}{\alpha - \beta}, \quad B_1 V_1 = \frac{(k_{21} - \beta)D}{\alpha - \beta}$$

$$Q_2(t_s) = A_2 V_2 e^{-\alpha t_s} + B_2 V_2 e^{-\beta t_s} \tag{5b}$$

$$A_2 V_2 = \frac{-k_{12}D}{\alpha - \beta}, \quad B_2 V_2 = \frac{k_{12}D}{\alpha - \beta}$$

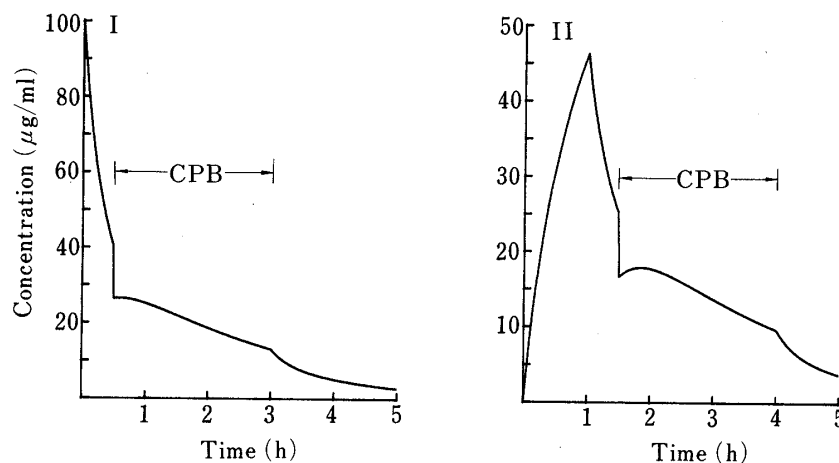


Fig. 2. Schematic Pharmacokinetic Profile Following Bolus Intravenous Injection (I) or One-Hour Constant Rate Intravenous Injection (II)

Reference values: $D=500$ mg, $V_1=5.0$ l, $V_p=2.5$ l, $k_{12}=1.2$ h⁻¹, $k_{21}=1.8$ h⁻¹, $k_e=1.2$ h⁻¹, $\mu=0.4$.

In the case that renal or hepatic failure does not occur during CPB, the serum concentration after the end of CPB follows the same time-course as that before the institution of CPB. That is, the time-course after the end of CPB is expressed by Eq. 6, where t_e represents the time at the end of CPB. The amounts of the drug in central and peripheral compartments at $t=t_e$ can be calculated from Eqs. 7a and 7b, respectively.

$$C_1 = A_1 e^{-\alpha(t-t_e)} + B_1 e^{-\beta(t-t_e)} \quad (6)$$

$$A_1 = \frac{(\alpha - k_{21})Q_1(t_e) - k_{21}Q_2(t_e)}{(\alpha - \beta)V_1}$$

$$B_1 = \frac{(k_{21} - \beta)Q_1(t_e) + k_{21}Q_2(t_e)}{(\alpha - \beta)V_1}$$

$$Q_1(t_e) = A_1 V_1 e^{-\alpha'(t_e-t_s)} + B_1 V_1 e^{-\beta'(t_e-t_s)} \quad (7a)$$

$$A_1 V_1 = \frac{\{(\alpha' - k_{21})Q_1(t_s) - k_{21}Q_2(t_s)\} V_1}{(\alpha' - \beta')(V_1 + V_p)}$$

$$B_1 V_1 = \frac{\{(k_{21} - \beta')Q_1(t_s) + k_{21}Q_2(t_s)\} V_1}{(\alpha' - \beta')(V_1 + V_p)}$$

$$Q_2(t_e) = A_2 V_2 e^{-\alpha'(t_e-t_s)} + B_2 V_2 e^{-\beta'(t_e-t_s)} \quad (7b)$$

$$A_2 V_2 = \frac{-\mu k_{12} Q_1(t_s) + (k_{21} - \beta') Q_2(t_s)}{\alpha' - \beta'}, \quad B_2 V_2 = \frac{\mu k_{12} Q_1(t_s) + (\alpha' - k_{21}) Q_2(t_s)}{\alpha' - \beta'}$$

In the case of constant rate intravenous infusion, drug concentrations in the central and peripheral compartments during infusion are given by Eqs. 8a and 9a, and those after the end of infusion are expressed by Eqs. 8b and 9b, respectively. In Eqs. 8 and 9, K is the constant infusion rate, t_0 is the infusion time and t' represents the

$$C_1 = A_1(1 - e^{-\alpha t}) + B_1(1 - e^{-\beta t}) + \frac{Q_1}{V_1} \quad (0 \leq t \leq t_0) \quad (8a)$$

$$C_1 = \left\{ \frac{(\alpha - k_{21})K}{(\alpha - \beta)\alpha V_1} - A_1 e^{-\alpha t_0} \right\} e^{-\alpha t'} + \left\{ \frac{(k_{21} - \beta)K}{(\alpha - \beta)\beta V_1} - B_1 e^{-\beta t_0} \right\} e^{-\beta t'} \quad (t \geq t_0) \quad (8b)$$

$$A_1 = \frac{(\alpha - k_{21})K}{(\alpha - \beta)\alpha V_1} - \frac{(\alpha - k_{21})Q_1 - k_{21}Q_2}{(\alpha - \beta)V_1}$$

$$B_1 = \frac{(k_{21} - \beta)K}{(\alpha - \beta)\beta V_1} - \frac{(k_{21} - \beta)Q_1 + k_{21}Q_2}{(\alpha - \beta)V_1}$$

$$C_2 = A_2(1 - e^{-\alpha t}) + B_2(1 - e^{-\beta t}) + \frac{Q_2}{V_2} \quad (0 \leq t \leq t_0) \quad (9a)$$

$$C_2 = \left\{ \frac{-k_{12}K}{(\alpha - \beta)\alpha V_2} - A_2 e^{-\alpha t_0} \right\} e^{-\alpha t'} + \left\{ \frac{k_{12}K}{(\alpha - \beta)\beta V_2} - B_2 e^{-\beta t_0} \right\} e^{-\beta t'} \quad (t \geq t_0) \quad (9b)$$

$$A_2 = \frac{-k_{12}V_1}{(\alpha - k_{21})V_2} A_1, \quad B_2 = \frac{k_{12}V_1}{(k_{21} - \beta)V_2} B_1$$

time since the end of infusion, that is, $t - t_0$. When the amounts of drug in the central and peripheral compartments are both zero at the start of infusion, both Q_1 and Q_2 in Eq. 8a become zero.

If the institution of CPB is during the infusion, the serum concentration-time course is expressed by the equation using $t - t_s$, α' , β' , μk_{12} , k_{21} , μk_e and $(V_1 + V_p)$ instead of t , α , β , k_{12} , k_{21} , k_e and V_1 in Eq. 8a, respectively. The values of $Q_1(t_s)$ and $Q_2(t_s)$ can be calculated by using Eqs. 10a and 10b, respectively.

$$Q_1(t_s) = A_1 V_1 (1 - e^{-\alpha' t_s}) + B_1 V_1 (1 - e^{-\beta' t_s}) \quad (10a)$$

$$A_1 V_1 = \frac{(\alpha - k_{21})K}{(\alpha - \beta)\alpha}, \quad B_1 V_1 = \frac{(k_{21} - \beta)K}{(\alpha - \beta)\beta}$$

$$Q_2(t_s) = A_2 V_2 (1 - e^{-\alpha' t_s}) + B_2 V_2 (1 - e^{-\beta' t_s}) \quad (10b)$$

$$A_2 V_2 = \frac{-k_{12}K}{(\alpha - \beta)\alpha}, \quad B_2 V_2 = \frac{k_{12}K}{(\alpha - \beta)\beta}$$

After the end of CPB, the serum concentration-time course is given by the equation using $t - t_e$ instead of t in Eq. 8a, and $Q_1(t_e)$ and $Q_2(t_e)$ can be calculated by using Eqs. 11a and 11b, respectively.

$$Q_1(t_e) = A_1 V_1 (1 - e^{-\alpha'(t_e - t_s)}) + B_1 V_1 (1 - e^{-\beta'(t_e - t_s)}) + \frac{V_1 Q_1(t_s)}{V_1 + V_p} \quad (11a)$$

$$A_1 V_1 = \frac{(\alpha' - k_{21})K V_1}{(\alpha' - \beta')\alpha'(V_1 + V_p)} - \frac{\{(\alpha' - k_{21})Q_1(t_s) - k_{21}Q_2(t_s)\} V_1}{(\alpha' - \beta')(V_1 + V_p)}$$

$$B_1 V_1 = \frac{(k_{21} - \beta')K V_1}{(\alpha' - \beta')\beta'(V_1 + V_p)} - \frac{\{(k_{21} - \beta')Q_1(t_s) + k_{21}Q_2(t_s)\} V_1}{(\alpha' - \beta')(V_1 + V_p)}$$

$$Q_2(t_e) = A_2 V_2 (1 - e^{-\alpha'(t_e - t_s)}) + B_2 V_2 (1 - e^{-\beta'(t_e - t_s)}) + Q_2(t_s) \quad (11b)$$

$$A_2 V_2 = \frac{-\mu k_{12}}{\alpha' - k_{21}} A_1 (V_1 + V_p), \quad B_2 V_2 = \frac{\mu k_{12}}{k_{21} - \beta'} B_1 (V_1 + V_p)$$

In the case that the institution of CPB is after the end of infusion, the serum concentration-time course can be evaluated by the same procedure as in the case of bolus intravenous injection taking into account the amounts of the drug in the central and peripheral compartments at $t = t_0$.

Two pharmacokinetic profiles are schematically illustrated in Fig. 2 when the same dose was administered intravenously by bolus injection and by one-hour constant rate infusion, and cardiopulmonary bypass was begun at 30 min after the end of infusion or injection and finished within 3 h after the end of drug administration. The reference values of D , V_1 , V_p , k_{12} , k_{21} , k_e and μ used for the preparation of the profiles are 500 mg, 5.0 l, 2.5 l, 1.2 h^{-1} , 1.8 h^{-1} , 1.2 h^{-1} and 0.4, respectively. In the profiles of Fig. 2, a peak is hardly recognized during CPB in the bolus injection but is clearly seen during CPB in the constant rate infusion, since the value of $Q_2(t_s)/Q_1(t_s)$ in the constant rate infusion is larger than that in the bolus injection. When in Eq. 3 the product of $-\alpha'$ and A_1' is larger than that of β' and B_1' , a peak is recognized in the profile during CPB.

Microbiological Assay—The serum concentrations of CTM were measured by the cyclinder-plate method using *P. mirabilis* ATCC-21100 as the indicator strain.⁵⁾

Results and Discussion

Two representative (A and B)⁶⁾ out of several patients, for whom an adequate prophylactic regimen of CTM for open-heart operation had been established, were selected

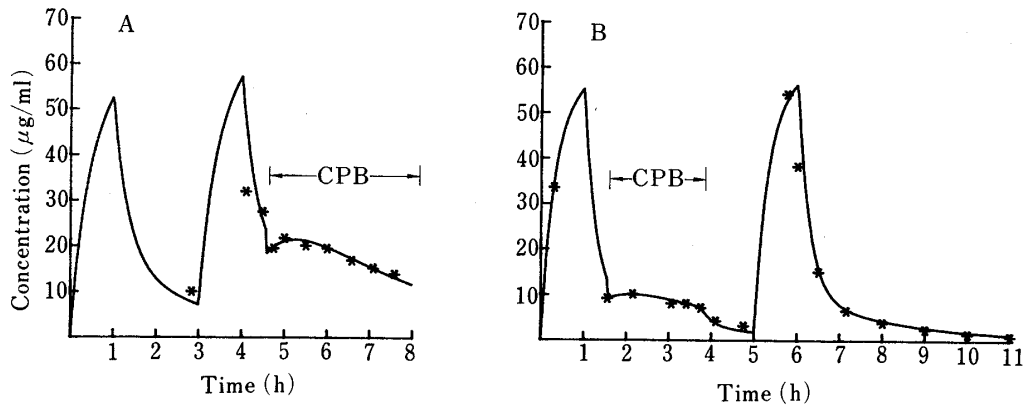


Fig. 3. Pharmacokinetic Profile of CTM Concentration in Serum of Patients A and B before, during and after CPB Surgery

TABLE I. Pharmacokinetic Parameters of CTM before, during and after CPB Surgery

| Patient | A | | B | |
|------------------------------|------------|---------------------|-----------|--------------------|
| | before CPB | during CPB | after CPB | during CPB |
| α (h^{-1}) | 2.95 | 1.36 | 3.56 | 1.26 |
| β (h^{-1}) | 0.45 | 0.31 | 0.41 | 0.35 |
| $t_{1/2\beta}$ (h) | 1.54 | 2.22 | 1.70 | 2.01 |
| k_{12} (h^{-1}) | 1.00 | 0.32 | 0.93 | 0.28 |
| k_{21} (h^{-1}) | 0.86 | 0.86 | 0.59 | 0.59 |
| k_e (h^{-1}) | 1.54 | 0.49 | 2.45 | 0.74 |
| V_1 (l) | 9.42 | 11.82 ^{a)} | 5.06 | 7.46 ^{a)} |
| Cl (ml/min) | 241.8 | 96.5 | 206.6 | 92.0 |
| μ | | 0.32 | | 0.30 |

a) The values are the sum of V_1 and V_p .

for the analysis of serum concentrations during CPB. On the day prior to the operation, candidate A received 20 mg/kg of CTM by one-hour constant rate intravenous infusion, and blood samples were collected at appropriate intervals. On the day of the operation, 20 mg/kg of CTM was administered three times to candidates A and B by one-hour constant rate intravenous infusion. The second infusion was started three hours after the first one and the third infusion was started five hours after the second one. Cardiopulmonary bypass was started about 1.5 h after the start of the second infusion and continued for 3.7 h for A and 2.2 h for B. Blood samples were taken from A mainly during CPB and from B during CPB and after the third infusion. The serum concentration–time data which were obtained on the day prior to the operation for A and after the third infusion on the day of the operation for B, were analyzed with the two-compartment open model. The pharmacokinetic parameters obtained from the analyses are shown in Table I. Next, the optimum values of parameter μ were determined by a least-squares method to minimize the sum of the squares of differences between the observed concentrations during CPB and the values calculated from Eq. 3 using the parameters in Table I and 2.4 l as the volume of priming solution. The optimum values of μ for A and B were determined as 0.32 and 0.30, respectively. Blood pressures during CPB were maintained at 80–100 mmHg for A and 60–90 mmHg for B, and both were a little lower than those before the open-heart operation (A, 80–130 mmHg; B, 60–120 mmHg). The optimum μ values of 0.32 for A and 0.30 for B are both smaller than the products of the

rate of dilution and the rate of decrease of blood pressure. The μ value will be affected not only by the rate of dilution and the rate of decrease of blood pressure but also by changes of physiological condition, such as the patient's temperature, during CPB.⁷⁾ The pharmacokinetic parameters during CPB are also shown in Table I, and pharmacokinetic profiles are shown in Fig. 3. It is clear from Fig. 3 that the simulated curves are in fair agreement with the observed concentrations. Table I shows that the values of serum clearance (Cl) during CPB for the two candidates are fairly small compared with those when CPB was not used. The results are consistent with a reduction in CTM elimination during CPB.

In the present paper, we were able to analyze successfully the serum concentrations during CPB using the simple model shown in Fig. 1-b. Strictly speaking, the value of k_{21} will also change more or less during CPB and the value of μ for k_e will not necessarily be equal to that for k_{12} . However, if the number of variables to be determined is increased, more serum concentration-time data will be necessary in order to obtain a reliable value of each variable. Such a model with many variables is not practical in clinical studies. The method reported in this paper should be useful for the analysis of serum concentrations during CPB, since the concentrations can be assessed by using the volume of priming solution V_p and only the variable μ when the pharmacokinetic parameters before or after CPB are available.

Further studies on the CTM kinetics during CPB are in progress.

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References and Notes

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- 4) In the present study, the priming solution for the cardiopulmonary pump-oxygenator consisted of 1400 ml of blood, 600 ml of Ringer's lactate and 400 ml of 10% mannitol.
- 5) T. Fugono and K. Maeda, *Chemotherapy*, **27**, Suppl. 3, 106 (1979).
- 6) Candidate A is a 51-year-old male with a creatinine clearance of 57 ml/min and weighing 62 kg. Candidate B is a 20-year-old female with a creatinine clearance of 83 ml/min and weighing 46 kg.
- 7) In the present study, the patient's temperature was lowered to 26 to 28 °C by use of the heat exchanger in the pump, in order to diminish metabolic activity and oxygen requirement.