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Preparation of Mean Drug Concentration–Time Curves in Plasma. A Study on the Frequency Distribution of Pharmacokinetic Parameters

EIJI MIZUTA* and ATSUKO TSUBOTANI

Central Research Division, Takeda Chemical Industries, Ltd., Jusohonmachi, Yodogawa-ku, Osaka 532, Japan

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A study on the frequency distribution of various pharmacokinetic parameters was conducted using pharmacokinetic data based on human blood samples obtained after administration of three cephalosporin derivatives. The results indicated that pharmacokinetic parameters k_a, k_e, V, α, β, k_{12}, k_{21}, V_1, V_d and Cl followed lognormal distribution curves rather than normal distribution curves. Thus, in the case of a one-compartment open model, it was demonstrated that mean plasma concentration–time curves could be prepared more precisely by use of the geometrical mean values of V, k_e and k_a. In the case of a two-compartment open model, the use of the geometrical mean values of V_1, α, β and k_e rather than those of V_1, k_{12}, k_{21} and k_e was considered to be preferable in view of the reliability of the rate constants α, β, k_{12} and k_{21}.

Keywords——pharmacokinetic analysis; mean plasma concentration–time curve; frequency distribution; pharmacokinetic parameter; arithmetic mean; geometrical mean; frequency histogram; observed frequency; expected frequency

The time course of the concentration of a drug in plasm (or serum) is useful as a guide for the administration of the drug. Therefore, it is usually the case that, prior to the clinical application of a drug, pharmacokinetic parameters are determined and the mean plasma concentration–time curve is simulated. In most cases the mean plasma concentration curve has been prepared by using arithmetic mean values of individual pharmacokinetic parameters such as rate constant and distribution volume.[1] However, there seem to be some problems in the method for calculating the mean value. That is, generally the mean half-life ($t_{1/2}(\overline{k_e})$) of the elimination phase calculated using the arithmetic mean value of individual elimination rate constants is not identical with the arithmetic mean value ($\overline{t_{1/2}(k_e)}$) of the individual half-lives. Similarly, the mean plasma clearance ($Cl=\overline{k_e}\times\overline{V_1}$) calculated using the product of the arithmetic mean value ($\overline{k_e}$) of individual elimination rate constants and that ($\overline{V_1}$) of individual apparent distribution volumes of the central compartment does not accord with the arithmetic mean value ($\overline{Cl}$) of the individual Cl values. Moreover, the mean value of the area under the plasma concentration–time curve (AUC) obtained by dividing dose (D) by $\overline{Cl}$ is also inconsistent with the arithmetic mean value ($\overline{AUC}$) of the individual AUC values.[1,2] For the preparation of a mean drug concentration–time curve in plasma, it has not been clear which pharmacokinetic parameters, rate constants or half-lives, and Cl or AUC, should be adopted and whether the arithmetic mean method is valid for the case that the distribution volumes are different.

In this paper, we shall discuss the frequency distributions of each pharmacokinetic parameter based on the results of pharmacokinetic analyses of human blood samples obtained after administration of one of three cephalosporins, *i.e.*, cefsulodin (CFS), cefotiam (CTM) and cefmenoxime (CMX). The preparation of mean plasma concentration–time curves based on the frequency distributions of the pharmacokinetic parameters is also

discussed.

Theoretical

The pharmacokinetic parameters commonly used for the one-compartment open model involve Cl, AUC, k_a (absorption rate constant), k_e, $t_{1/2}(k_e)$ and V (apparent volume of distribution). On the other hand, for the case of a two-compartment open model, hybrid rate constants α and β, their half-lives $t_{1/2}(\alpha)$ and $t_{1/2}(\beta)$, transfer rate constants k_{12} and k_{21}, k_e, V_1 and V_d (apparent volume of distribution of β-phase) are used in addition to Cl, AUC and k_a. In this paper, p, q and r are hereafter employed instead of k_{12}, k_{21} and k_e of the two-compartment open model, respectively. As is clear from the *in vitro* simulation model,[3,4] the parameters which are directly related to the plasma concentration–time curves are rate constants, clearance constants and distribution volumes. When mean plasma concentration–time curves are prepared, there is a possibility that a discrepancy may arise between the curves depending on which of the two parameters, the arithmetic mean of individual rate constants or that of individual clearance constants, is used. As for rate constants, there seem to be some difficulties in the use of the mean values determined independently of the individual distribution volumes. Therefore, it would be preferable to adopt the mean values of clearance constants, which are given by the product of the distribution volume and the rate constant. For distribution volumes such as V, V_1 and V_d, the arithmetic mean of individual values is also adopted. Given the above two assumptions, the parameters for preparing mean plasma concentration–time curves can be calculated from Eqs. 1, 2 and 3 for the one-compartment

$$V=\sum_{i=1}^{n} V_i/n=\overline{V_i} \tag{1}$$

$$Cl=\sum_{i=1}^{n} Cl_i/n=\overline{Cl_i} \tag{2}$$

$$k_e=\overline{Cl_i}/\overline{V_i} \tag{3}$$

$$k_a=\left(\sum_{i=1}^{n} k_{ai}V_{kai}/n\right)\Big/\left(\sum_{i=1}^{n} V_{kai}/n\right)=\overline{Cl_i}/\overline{V_{kai}} \tag{4}$$

open model. By assuming the apparent volume of distribution at the absorption site used in the *in vitro* simulation model to be $V_{ka}=Cl/k_a$, the parameter k_a is obtained from Eq. 4 by dividing the arithmetic means of individual Cl's by that of individual V_{ka}'s. In the case of a two-compartment open model, the simulation curve is obtained by calculation using either the combination of α, β, r and V_1, or that of p, q, r and V_1. The parameters V_1, β, p and r are calculated from Eqs. 5—8, respectively. The parameters α and q are obtained from Eqs. 9 and 10, by assuming the apparent volume of distribution of α-phase to be $V_\alpha=Cl/\alpha$ and that of the

$$V_1=\sum_{i=1}^{n} V_{1i}/n=\overline{V_{1i}} \tag{5}$$

$$\beta=\left(\sum_{i=1}^{n} \beta_i V_{di}/n\right)\Big/\left(\sum_{i=1}^{n} V_{di}/n\right)=\overline{Cl_i}/\overline{V_{di}} \tag{6}$$

$$p=\left(\sum_{i=1}^{n} p_i V_{1i}/n\right)\Big/\overline{V_{1i}}=\overline{p_i V_{1i}}/\overline{V_{1i}} \tag{7}$$

$$r=\overline{Cl_i}/\overline{V_{1i}} \tag{8}$$

$$\alpha=\left(\sum_{i=1}^{n} \alpha_i V_{\alpha i}/n\right)\Big/\left(\sum_{i=1}^{n} V_{\alpha i}/n\right)=\overline{Cl_i}/\overline{V_{\alpha i}} \tag{9}$$

$$q=\overline{p_i V_{1i}}/\overline{V_{2i}} \quad (10)$$

second compartment to be $V_2=pV_1/q$. In order to apply the rate constants and distribution volumes obtained from Eqs. 1—10 for the preparation of mean plasma concentration–time curves, it is essential that individual values of V, V_1, V_2, V_d, V_α, V_{ka}, Cl and pV_1 (permeability coefficient for transfer of the drug from the first compartment to the second compartment[5]) are normally distributed. On the other hand, if individual values of V and k_e, and V_1, V_d, r and β follow a normal distribution, the values of Cl should be calculated as the product of the arithmetic mean of individual distribution volumes and that of individual rate constants.

Experimental

Plasma Concentration Data——Blood samples were obtained from patients or volunteers, to whom one of three cephalosporins (CFS, CTM and CMX; Takeda Chemical Industries) had been administered. The serum concentrations of CFS, CTM and CMX were measured according to Fugono[6] by the cylinder-plate method using *P. aeruginosa* NCTC-10490 (for CFS) or *P. mirabilis* ATCC-21100 (for CTM and CMX) as the indicator strain. Serum drug concentration data for a subject having normal renal function measured at more than five intervals after administration were used for the pharmacokinetic analyses.

Pharmacokinetics——Pharmacokinetic evaluation was performed using an improved version of our computer program reported earlier.[7] The optimum values of parameters A, k_a, and k_e for the one-compartment open model and A_1, B_1, k_a, α and β for the two-compartment open model were determined by the combined use of a least-squares method and a steepest descent method to minimize the sum of weighted squares of differences between the observed values and the values calculated from standard equations such as Eq. 11, an equation for the two-compartment open model with bolus intravenous injection. The reciprocals of individual serum concentrations were mainly adopted for the weights.

$$C_1=A_1e^{-\alpha t}+B_1e^{-\beta t} \quad (11)$$

Results

The serum concentration data obtained from 276 subjects were adopted for the pharmacokinetic analyses. Numbers of subjects classified according to drug, dose and route of administration are shown in Table I. The serum concentrations of CFS, CTM and CMX after intravenous administrations were analyzed according to the two-compartment open model. The 89 data for intramuscular injection were analyzed according to the one-compartment

Table I. Numbers of Samples Classified According to Drug, Dose and Route of Administration

	CFS	CTM	CMX		CFS	CTM	CMX
I.V.[a]				D.I.[b]			
125 mg		2		500 mg/0.5 h			4
250 mg		3	4	1000 mg/0.5 h	15	2	
500 mg	6	14	9	250 mg/1.0 h			4
1000 mg	2	7	42	500 mg/1.0 h	4		7
				1000 mg/1.0 h	2	12	28
I.M.[c]				2000 mg/1.0 h	2	5	5
125 mg	3	3		1000 mg/2.0 h		6	
250 mg	12	13	4	2000 mg/2.0 h			2
500 mg	29	10 (3)[d]	9 (9)				
1000 mg		3 (3)	3 (3)				

a) Bolus intravenous injection. *b*) Constant rate intravenous infusion. *c*) Intramuscular injection. *d*) The numbers in parentheses show numbers of samples analyzed according to the two-compartment open model.

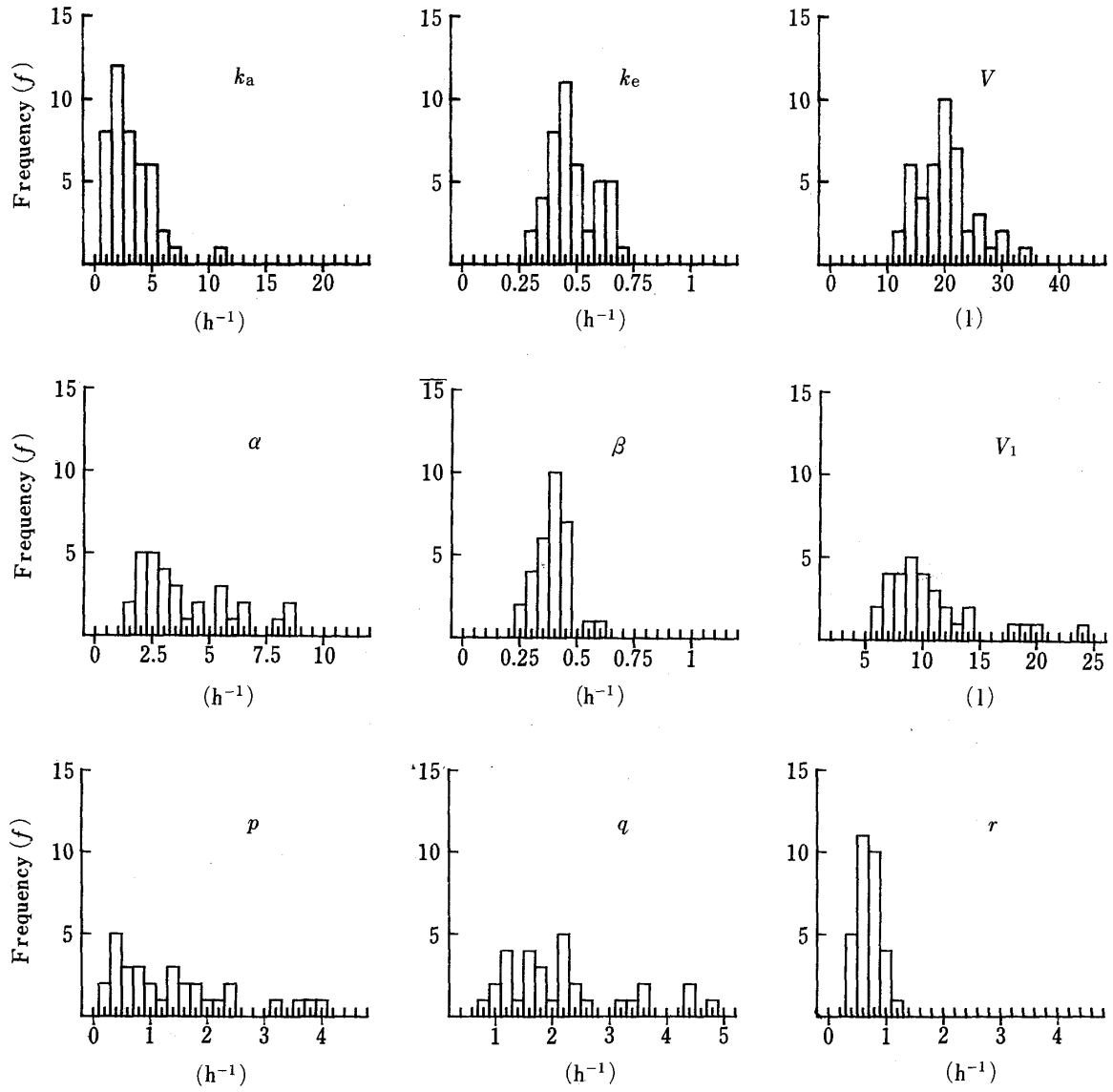

Fig. 1. Histograms of Pharmacokinetic Parameters for Cefsulodin

There are 44 data for k_a, k_e and V analyzed by the one-compartment open model, and 31 data for α, β, V_1, p, q and r analyzed by the two-compartment open model.

open model, since the number of measurements for one sample was not adequate to estimate the first-order absorption rate constant (k_a) and the rate constant (α) of the α-phase. However, the data for 18 samples out of 89, which consisted of more than six measurements, were also analyzed according to the two-compartment open model. Frequency histograms of k_a, k_e and V obtained by the analyses of 89 samples are shown in Figs. 1, 2 and 3 for CFS, CTM and CMX, respectively. The parameters α, β, V_1, $p(k_{12})$, q (k_{21}), and r (k_e) were obtained from analyses based on the two-compartment open model for the data of 205 subjects, of which 89 had received bolus intravenous injection, 98 constant rate intravenous infusion and 18 intramuscular injection. Frequency histograms of these parameters are also shown in Figs. 1, 2 and 3. The test for the normality of an observed frequency distribution usually requires data of at least 50 samples.[8] Therefore, the frequency distributions of each pharmacokinetic parameter were studied by the combined use of the parameters obtained for the three cephalosporin antibiotics.

In this case, however, it is required that the elimination, distribution and absorption of the

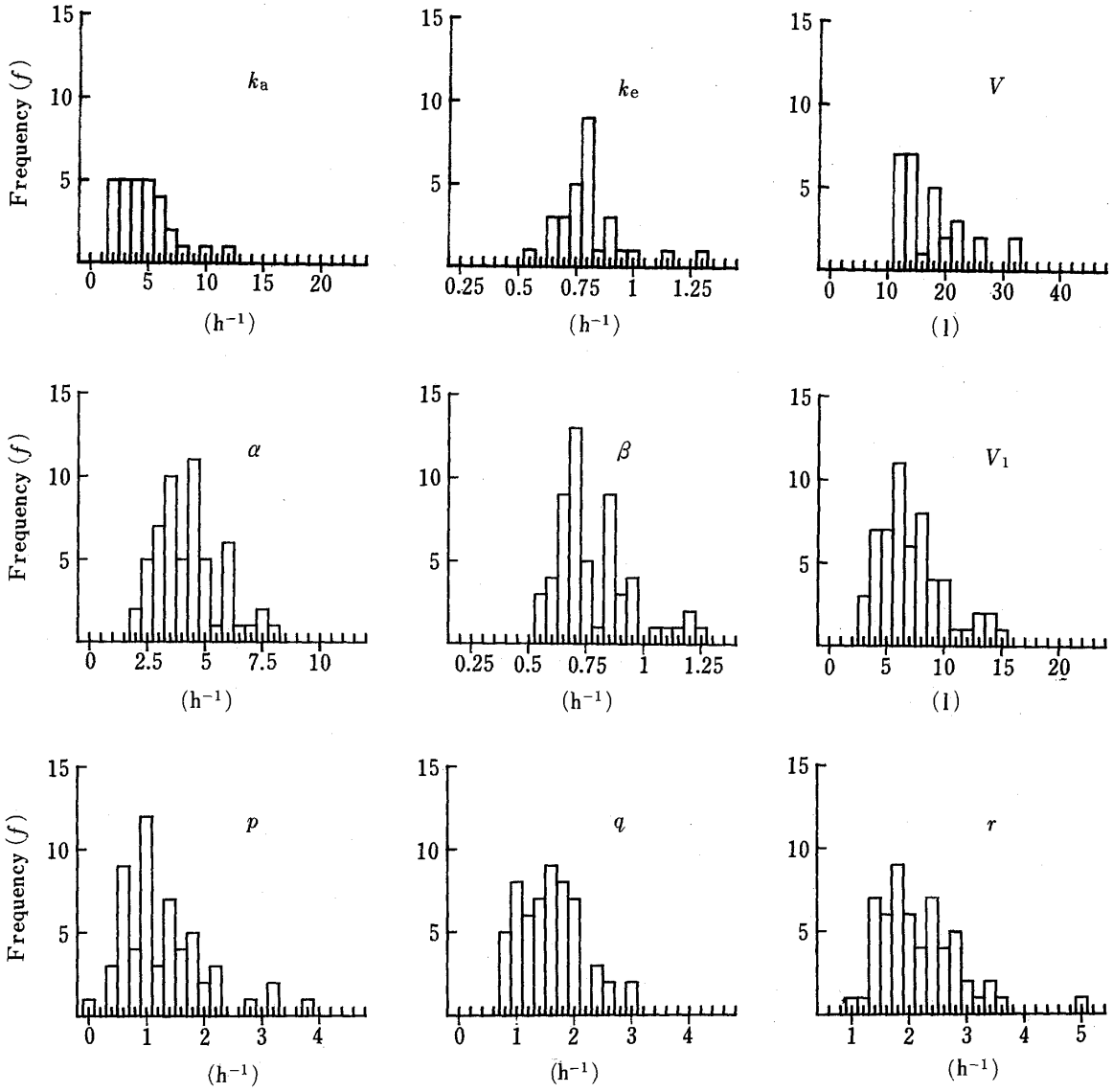

Fig. 2. Histograms of Pharmacokinetic Parameters for Cefotiam

There are 29 data for k_a, k_e and V analyzed by the one-compartment open model, and 57 data for α, β, V_1, p, q and r analyzed by the two-compartment open model.

drugs follow linear pharmacokinetics under the experimental conditions. The serum clearance (Cl), mean residence time ($MRT_{iv}=(p+q)/qr$) and steady-state volume of distribution ($V_{ss}=(p+q)V_1/q$) were calculated by using the pharmacokinetic parameters after bolus intravenous injection. The mean residence time ($MRT_{im}=(k_a+k_e)/k_ak_e$) and mean absorption time ($MAT_{im}=MRT_{im}-MRT_{iv}$) were also calculated from the data after intramuscular injection. These results are summarized in Table II with F-values obtained from the analysis of variance for Cl, MRT_{iv}, V_{ss} and MRT_{im}. When capacity-limited elimination and distribution occur, the increase of dose makes MRT_{iv} increase and makes Cl and V_{ss} decrease.[9] On the other hand, when capacity-limited absorption occurs, MAT_{im} values increase as the dose increases.[10] The results in Table II show that the dose level factors of the three cephalosporins were insignificant for Cl, MRT_{iv}, V_{ss} and MRT_{im}, indicating that these parameters were independent of the dose. MAT_{im} values for CTM and CMX were also independent of the dose. Therefore, the elimination, distribution and absorption of CFS, CTM and CMX may be considered to follow linear pharmacokinetics under the present experimental conditions.

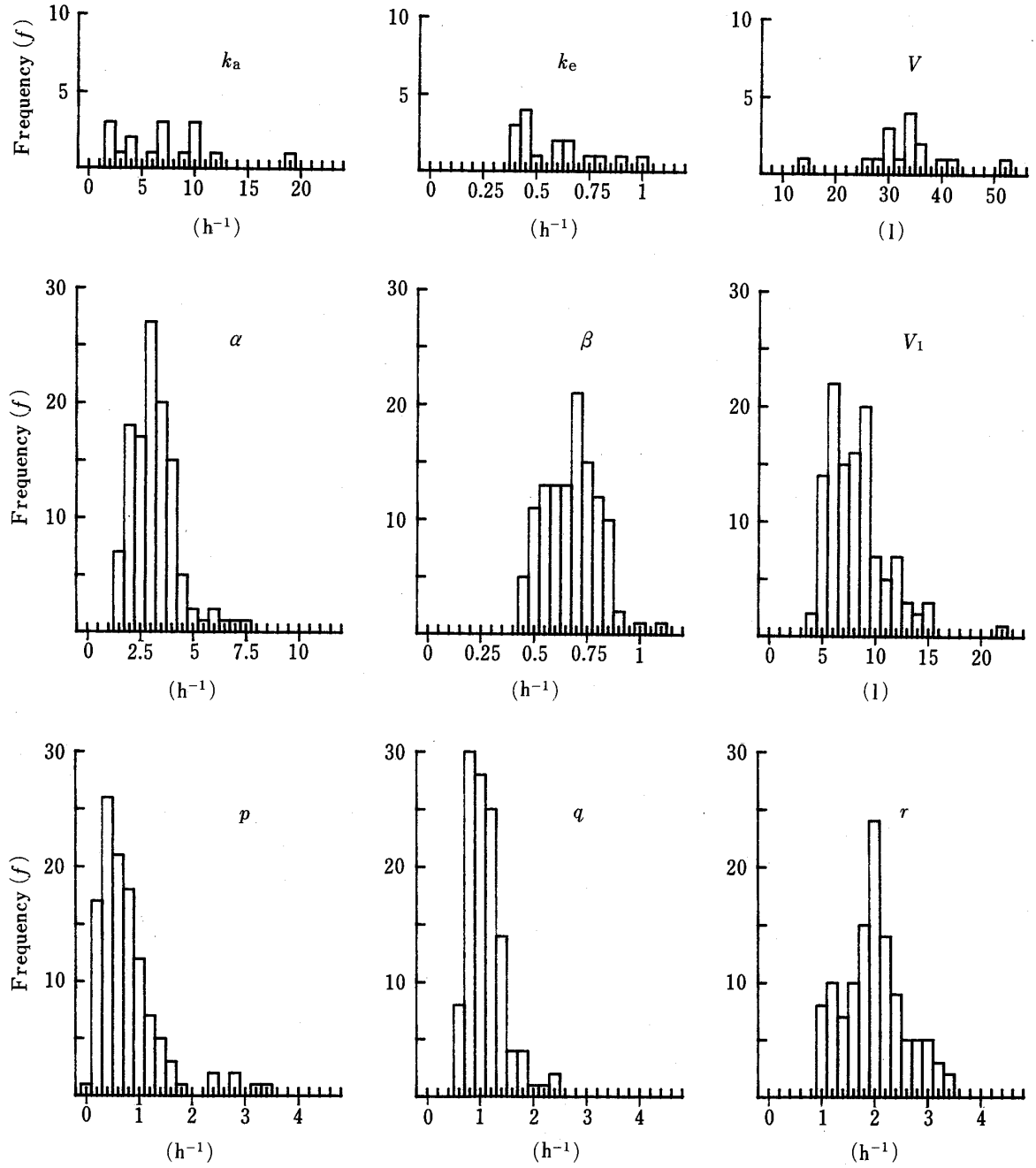

Fig. 3. Histograms of Pharmacokinetic Parameters for Cefmenoxime

There are 16 data for k_a, k_e and V analyzed by the one-compartment open model, and 117 data for α, β, V_1, p, q and r analyzed by the two-compartment open model.

In the combined use of the parameters obtained for the three cephalosporins, variations of each parameter resulting from differences in dose, route of administration, and drug should be eliminated.[11] For this purpose, arithmetic mean values of individual pharmacokinetic parameters in Figs. 1, 2 and 3 were calculated for each group classified for drug, dose, and route of administration as shown in Table I. Then individual values of the parameters were normalized by dividing the values by the mean values of the corresponding parameters within the same group. Furthermore, individual values of Cl, V_{ka}, V_d, V_α, V_2 and pV_1 were estimated from the parameters in Figs. 1, 2 and 3, and normalized in the same way. In the preparation of frequency histograms of the normalized values of individual parameters, three kinds of scale intervals (0.05, 0.1 and 0.2) were used taking into account the standard

TABLE II. *Cl*, *MRT*, V_{ss} and *MAT* after Administration of CFS, CTM and CMX

	Dose (mg)	*n*	I.V.[a] *Cl* (ml/min)	*MRT* (h)	V_{ss} (l)	*n*	I.M.[b] MRT_{im} (h)	MAT_{im} (h)
CFS	125					3	2.42±0.28	
	250					12	2.44±0.32	
	500	6	172±79[c]	2.08±0.36	21.2±10.4	29	2.79±0.53	0.71
	1000	2	107± 6	2.22±0.34	14.1± 1.5			
F[d]			1.22	0.231	0.835		2.78	
CTM	125	2	227±46	0.67±0.05	9.1± 1.2	3	1.34±0.17	0.67
	250	3	219±24	0.75±0.09	9.6± 0.8	13	1.57±0.19	0.82
	500	14	251±58	0.94±0.16	14.1± 3.8	10	1.53±0.13	0.59
	1000	7	234±32	0.89±0.24	12.1± 1.8	3	1.59±0.65	0.70
F			0.495	1.99	2.96		0.780	
CMX	250	4	220±54	0.82±0.13	10.3± 1.8	4	2.13±0.51	1.31
	500	9	257±31	0.85±0.19	12.9± 2.1	9	2.25±0.28	1.40
	1000	42	235±54	0.79±0.14	11.0± 2.5	3	1.80±0.19	1.01
F			0.939	0.639	2.65		2.00	

a) Bolus intravenous injection. *b*) Intramuscular injection. *c*) Arithmetic mean±standard deviation. *d*) *F*-value (F_6^1 (0.05)=5.99, F_{41}^2 (0.05)=3.22, F_{22}^3 (0.05)=3.05, F_{25}^3 (0.05)=2.99, F_{52}^2 (0.05)=3.17, F_{13}^2 (0.05)=3.81).

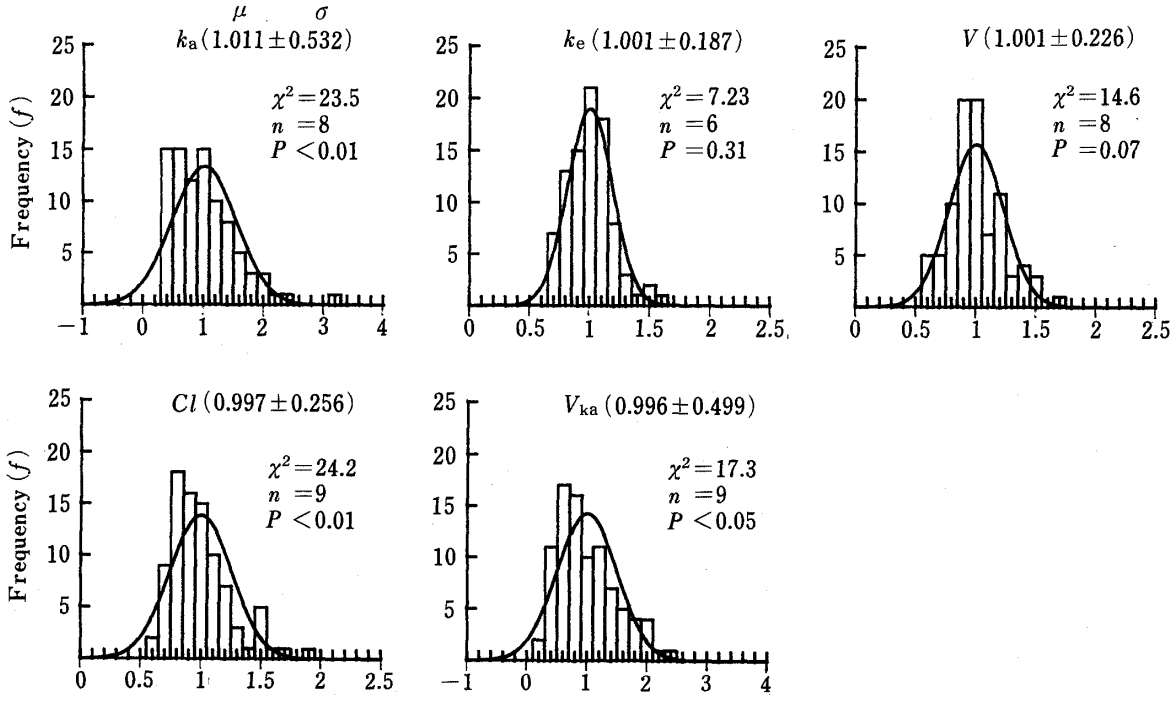

Fig. 4. Histograms of the Pharmacokinetic Parameters k_a, k_e, *V*, *Cl* and V_{ka} Normalized in Each Group Shown in Table I

In each histogram, the sum of frequencies is 89.

deviations (σ). The frequency histograms of normalized k_a, k_e, *V*, *Cl* and V_{ka} are shown in Fig. 4 and those of normalized α, β, V_1, *p*, *q*, *r*, *Cl*, V_α, V_d, V_2 and pV_1 are shown in Fig. 5. Normal distribution curves were computed from the means (μ) and variances (σ^2) estimated from each histogram using Eq. 12,[8] and are drawn over each histogram in Figs. 4 and 5. In Eq. 12, ϕ, *N*, and ω represent the expected number of samples at any given value of the continuous variate *y*, the total number of samples, and the width of the scale interval in the

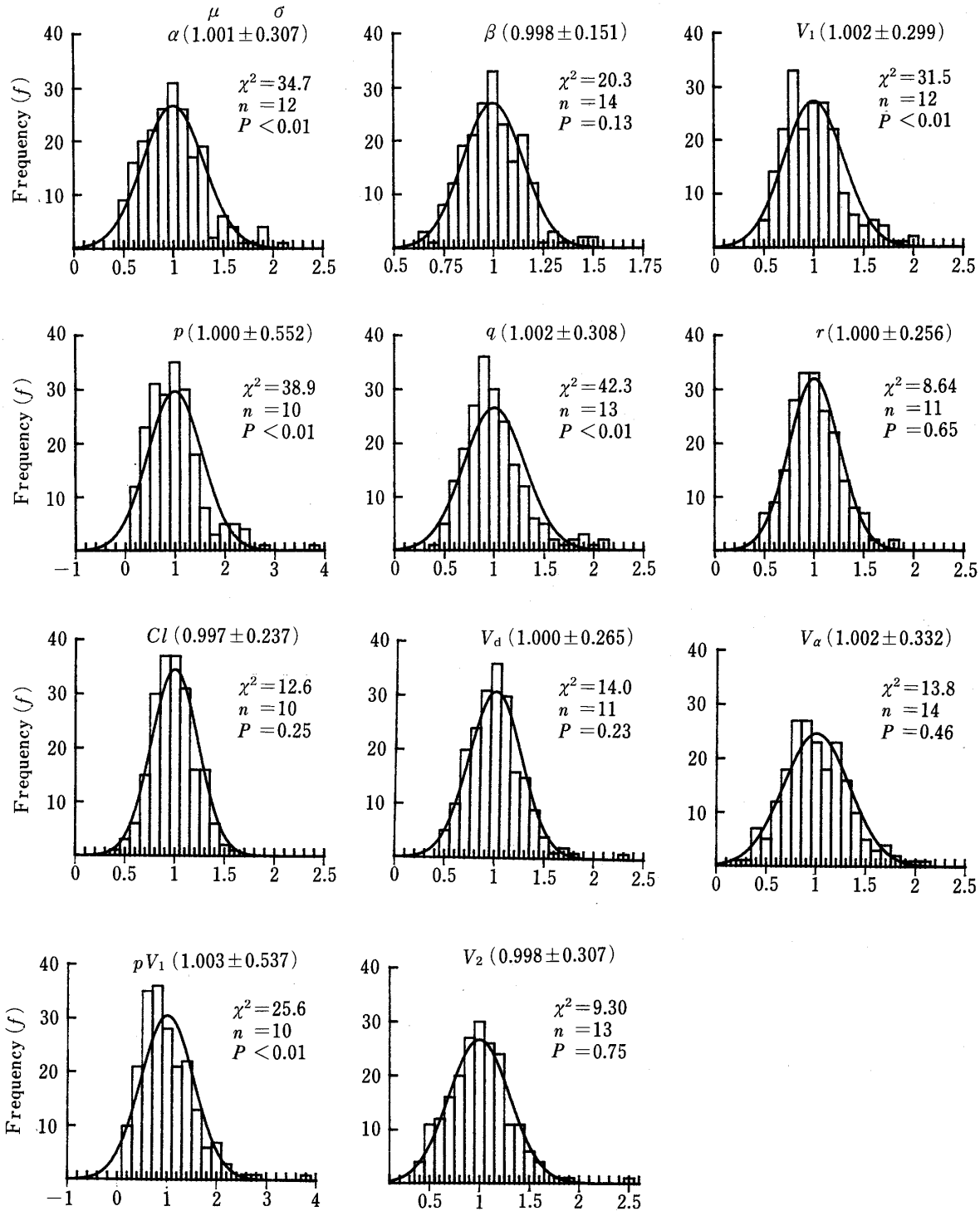

Fig. 5. Histograms of the Pharmacokinetic Parameters α, β, V_1, p, q, r, Cl, V_d, V_α, pV_1 and V_2 Normalized in Each Group Shown in Table I

In each histogram, the sum of frequencies is 205.

histogram, respectively. Therefore, $N\omega$ is equal to the area of the frequency histogram.

$$\phi=\frac{N\omega}{\sigma\sqrt{2\pi}}\,e^{-(1/2)(y-\mu)^2/\sigma^2} \tag{12}$$

On the other hand, logarithmic values of individual parameters were calculated for all the samples, and arithmetic mean values of them were obtained for each group mentioned above.

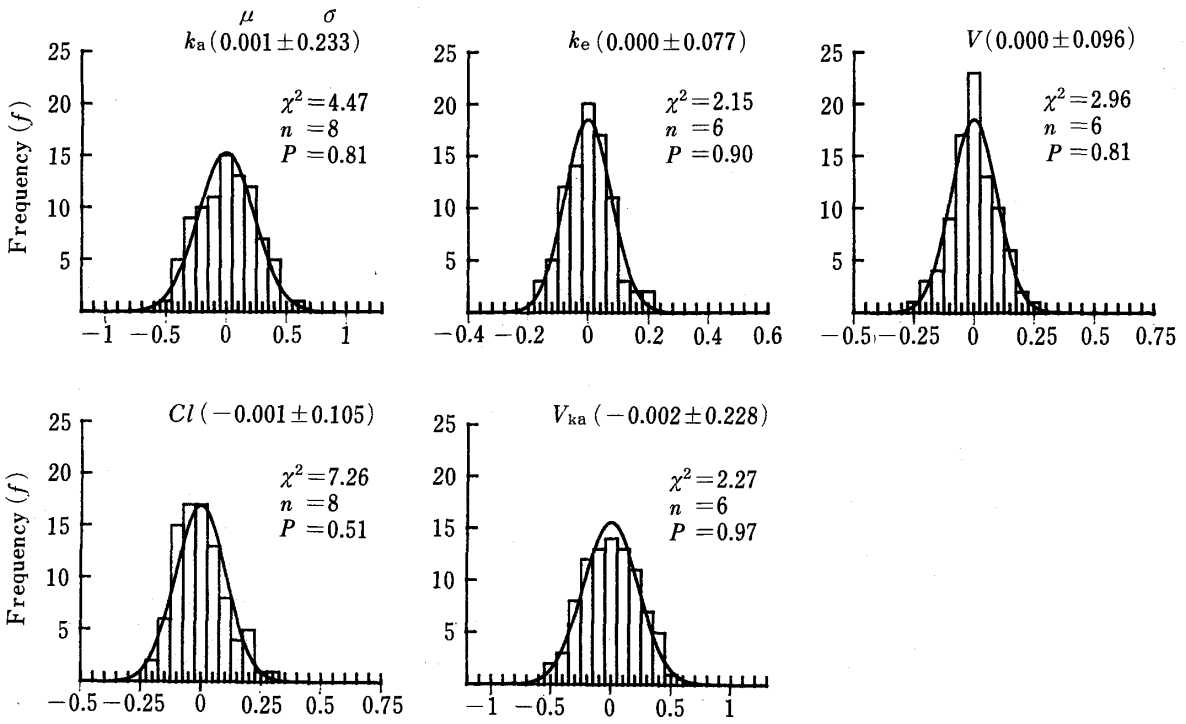

Fig. 6. Histograms of the Pharmacokinetic Parameters k_a, k_e, V, Cl and V_{ka} Normalized with the Logarithmic Values

In each histogram, the sum of frequencies is 89.

The scale for the mean values was determined as zero in order to eliminate the differences among the groups. Then frequency histograms of the logarithmic values for individual parameters were drawn with scale intervals of either 0.02 or 0.025, 0.04 or 0.05, and 0.08 or 0.10, corresponding to those in Figs. 4 and 5, *i.e.*, 0.05, 0.10, 0.20, respectively. Frequency histograms for k_a, k_e, V, Cl and V_{ka} are shown in Fig. 6, and those for α, β, V_1, p, q, r, Cl, V_α, V_d, V_2 and pV_1 in Fig. 7. Lognormal distribution curves, which were computed with Eq. 12 using the means and variances estimated from the histograms in Figs. 6 and 7, are drawn over the individual histograms. The χ^2 values were computed with Eq. 13[8] in order to test the normalities of individual frequency distributions in Figs. 4—7. In Eq. 13, f_i and ϕ_i respectively

$$\chi^2 = \sum_{i=1}^{K} (f_i - \phi_i)^2/\phi_i \qquad (13)$$

represent the observed and expected frequencies at the i-th scale interval, and K is the number of pairs of f_i and ϕ_i. At the ends of the distribution where ϕ_i is less than one, both ϕ_i's and the corresponding f_i's were summed over adjacent grouping intervals until the sum of ϕ_i exceeded one. The degree of freedom (DF) in χ^2 is equal to K-3, where 3 corresponds to the three fitted constants, N, μ, and σ. The numbers of DF (n) and χ^2 values computed with Eq. 13 are shown beside the histograms in Figs. 4—7 along with the probability value P. The discrepancies between the observed and expected frequencies in normal distributions of k_a and Cl in Fig. 4 and α, V_1, p, q and pV_1 in Fig. 5 were highly significant ($P<0.01$), and that for V_{ka} in Fig. 4 was also significant ($P<0.05$). Moreover, in the case of k_a, V_{ka}, p and pV_1, more than one frequency was expected in the negative region of the normal distribution curve, although rationally their observed values cannot be less than zero. Thus, normality of the frequency distributions of the eight parameters was rejected at a highly significant probability level. The discrepancies between the observed and the expected frequencies in normal distributions of k_e and V in Fig. 4 and β, r, Cl, V_α, V_d and V_2 in Fig. 5 were well within the error for random

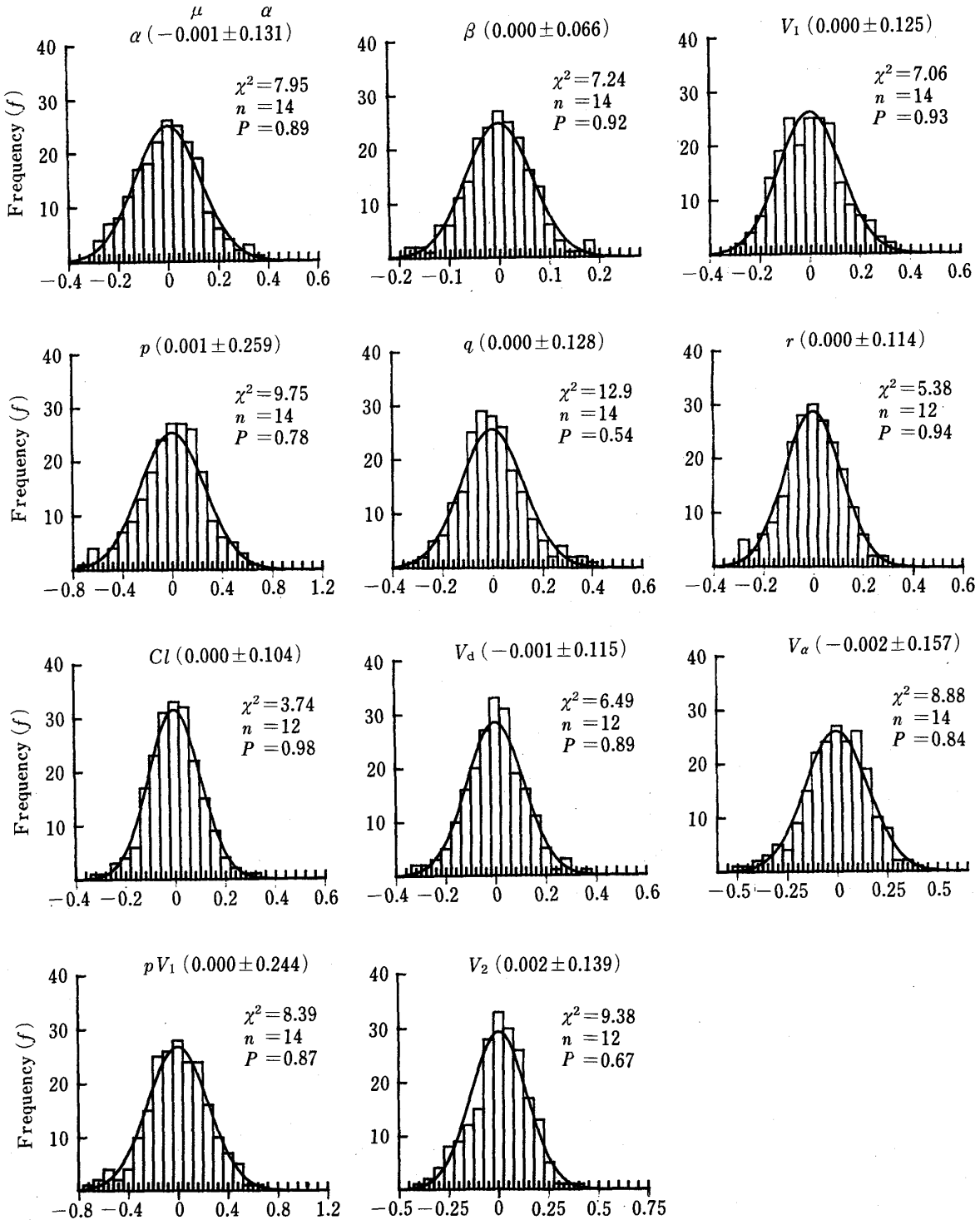

Fig. 7. Histograms of the Pharmacokinetic Parameters α, β, V_1, p, q, r, Cl, V_d, V_α, pV_1 and V_2 Normalized with the Logarithmic Values

In each histogram, the sum of frequencies is 205.

sampling from a normal population, since P values of the parameters were larger than 0.05. However, more than one frequency was observed in the region more than 3σ apart from the mean in every frequency histogram for the eight parameters. In such a case, possible non-normality might be concealed by the pooling of the end frequencies in computing χ^2. Thus the normalities of the frequency distributions of these eight parameters were also doubtful in spite

of their large P values.

On the other hand, the observed frequencies in lognormal distributions of every parameter in Figs. 6 and 7 agreed very well with the expected ones, as is clear from their P values. All P values based on lognormal distributions of these parameters, with the exception of V_2, were larger than those based on normal distributions. In the case of V_2, no frequency existed outside the range of 3σ from the mean in the histogram based on the lognormal distribution, although the P value was small compared with the case of normal distribution.

From these results, it would be more reasonable to consider that the pharmacokinetic parameters k_a, k_e, V, α, β, p, q, r, V_1, V_d and Cl (k_eV and rV_1), as well as the parameters V_{ka}, V_2, V_α and pV_1 which were derived from the *in vitro* simulation models, follow lognormal distribution curves rather than normal distribution curves. The half-lives ($t_{1/2}(x)$) and the area under the plasma (or serum) concentration–time curve (AUC), which are related to rate constants and plasma (or serum) clearance (Cl) by Eqs. 14 and 15, respectively, were also

$$\log t_{1/2}(x) = -\log x + \log(\ln 2) \tag{14}$$

x: k_e, α, β, p, q, r

$$\log AUC = -\log Cl + \log D \tag{15}$$

presumed to be distributed lognormally, since the logarithmic values of the half-lives and the rate constants, and those of AUC and Cl were distributed symmetrically about $\log(\ln 2)$ and $\log D$, respectively. The above results are consistent with the conclusion by Masuyama[12] that interindividual differences in a variety of medical data, such as steady-state blood concentrations of enzymes, hormones, heavy metals and drugs, followed lognormal distribution curves.

Thus, the mean values of the parameters Cl, V, V_{ka}, V_1, V_d, V_2, V_α and pV_1, which are used for the preparation of mean plasma concentration–time curves, should be calculated by the geometrical mean method. In this case, rate constants k_a and k_e, for example, which are calculated by dividing the geometrical mean of individual Cl by that of individual V_{ka} and V, respectively, are also obtained by using the geometrical mean of individual k_a and k_e as shown by Eqs. 16 and 17, respectively. Similarly, rate constants α, β, p, q and r are also obtained by

$$k_a = \frac{\sqrt[n]{Cl_1 Cl_2 \cdots Cl_n}}{\sqrt[n]{V_{ka1} V_{ka2} \cdots V_{kan}}} = \frac{\sqrt[n]{k_{a1} V_{ka1} k_{a2} V_{ka2} \cdots k_{an} V_{kan}}}{\sqrt[n]{V_{ka1} V_{ka2} \cdots V_{kan}}} = \sqrt[n]{k_{a1} k_{a2} \cdots k_{an}} \tag{16}$$

$$k_e = \frac{\sqrt[n]{Cl_1 Cl_2 \cdots Cl_n}}{\sqrt[n]{V_1 V_2 \cdots V_n}} = \sqrt[n]{k_{e1} k_{e2} \cdots k_{en}} \tag{17}$$

using the geometrical mean of individual values. Therefore, in the case of a one-compartment open model, it would be reasonable to prepare the mean plasma concentration–time curve by use of the geometrical mean values of V, k_e and k_a. Similarly, in the case of a two-compartment open model, the use of the geometrical means of V_1, r, α and β or those of V_1, r, p and q would be reasonable. In this case, the Cl value computed from the mean plasma concentration–time curve is equal not only to the geometrical mean of individual Cl values, but also to the products of the individual geometrical means of k_e and V, r and V_1, and β and V_d. The half-life and AUC computed from the mean curve are equal to the values obtained from Eqs. 14 and 15 by using the geometrical means of rate constant and Cl, respectively. Moreover, the geometrical means of individual half-lives and AUC values are also equal to the half-life and AUC computed from the mean curve, respectively.

For reference, a pair of mean serum concentration–time curves prepared by using the arithmetic and geometrical mean values of pharmacokinetic parameters in the case of 1000 mg CFS administration over 30 min by intravenous drip infusion[13] are shown in Fig. 8 together

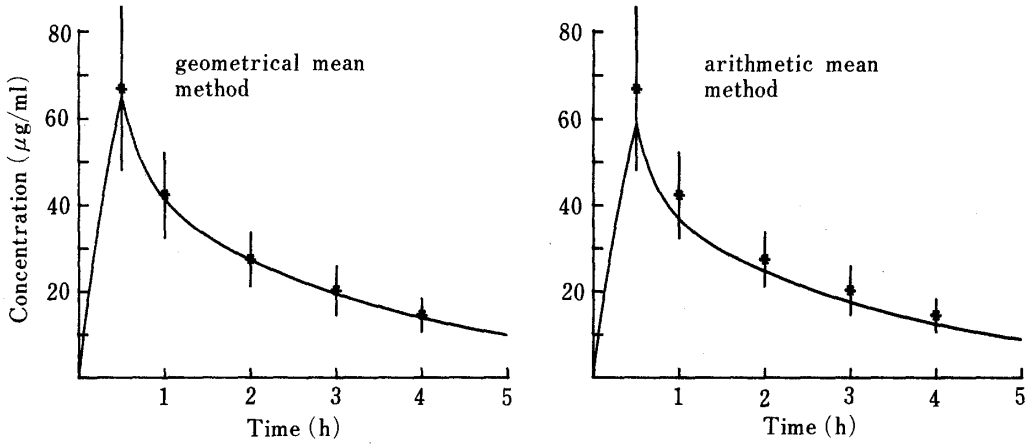

Fig. 8. Comparison of Mean Serum Concentration–Time Curves Following 1000 mg CFS Administration over 30 min by Intravenous Drip Infusion

Points are averages of 15 subjects and vertical lines represent standard deviations.

with the observed serum concentrations (mean ± S.D.). It can be seen that the curve obtained by the geometrical mean method agrees more closely with the observed values than the curve obtained by the arithmetic mean method.

Discussion

In the two-compartment open model for bolus intravenous injection, the pharmacokinetic parameters p, q, r, V_1, Cl and AUC are calculated from Eqs. 18—23,[14] respectively, by using the dose (D) and the optimum values of α, β, A_1 and B_1 obtained by the method mentioned in the experimental section. In this case, several serum concentration data

$$p=A_1B_1(\alpha-\beta)^2/(A_1+B_1)(\beta A_1+\alpha B_1) \quad (18)$$

$$q=(\beta A_1+\alpha B_1)/(A_1+B_1) \quad (19)$$

$$r=\alpha\beta(A_1+B_1)/(\beta A_1+\alpha B_1) \quad (20)$$

$$V_1=D/(A_1+B_1) \quad (21)$$

$$Cl=\alpha\beta D/(\beta A_1+\alpha B_1) \quad (22)$$

$$AUC=(\beta A_1+\alpha B_1)/\alpha\beta \quad (23)$$

measured with an appropriate interval shortly after injection are necessary in order to obtain accurate values of α and A_1. However, it is practically impossible to take several blood samples from human subjects within a short period after injection. On the other hand, serum concentration data are sufficient to estimate reasonably accurate values of β and B_1. Therefore, β is estimated more precisely than α, as is clear from the σ values of α ($\sigma=0.131$) and β ($\sigma=0.066$) in Fig. 7. The value of V_1 calculated from Eq. 21 is also affected mainly by the concentrations of blood samples taken within a short time after injection. Therefore, the σ value of 0.125 for V_1 in Fig. 7 is nearly equal to that of α. The accuracy of AUC, which is mainly affected by errors in the calculation of A_1/α, is better than that of α, since errors in computing α and A_1 are cancelled out in the calculation of A_1/α by the positive correlation existing between both errors. Therefore, the σ value of 0.104 for Cl given by D/AUC is smaller than those of α and V_1. The σ value of 0.114 for r given by Cl/V_1 approximates to that of V_1, and the values of 0.128 for q given by $\alpha\beta/r$ is nearly equal to that of α. The most complicated relation exists between the transfer rate constant p and the constants α, β, A_1 and B_1, as shown

in Eq. 18. Thus, errors in computing α, β, A_1, and B_1 are involved in the calculation of p, as is clear from the large σ value of 0.259. A parameter with such a large σ as p is not suitable to be used in the preparation of mean serum (or plasma) concentration–time curves. Therefore, in the preparation of mean serum (or plasma) concentration–time curves based on the two-compartment open model, it would be more reasonable to use the geometrical mean values of V_1, α, β and r than those of V_1, p, q and r.

Serum concentration data after intramuscular injection can often be analyzed satisfactorily by using the one-compartment open model, since the concentration data for an absorption phase and an α-phase are not measured frequently enough to estimate precise k_a and α values, and the α-phase is often concealed by the absorption phase because of the relatively small value of k_a compared to α. In the present paper, the frequency histogram of k_a in the two-compartment model could not be prepared, since only 18 out of 89 samples which were administered intramuscularly were analyzed according to the two-compartment open model. However, it can be readily predicted by analogy with the lognormal distribution of k_a in the one-compartment model that the logarithmic values of k_a are also distributed normally in the two-compartment model.

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