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Statistical Study of the Model-independent Method to describe the Blood Disappearance Profile of Intravenously Administered Drugs

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The applicability of the model-independent method to pharmacokinetic analysis was statistically studied. For this purpose, two kinds of data were used, *i.e.*, plasma disappearance data for warfarin (a typical example of a triple-exponential decay) and for amoxicillin (double-exponential decay). By using statistical analysis with least-squares fitting (SALS), a nonlinear regression analysis program, curve fittings were carried out with respect to those data sets. In the case of the warfarin data, the triple-exponential equation was superior to the model-independent one in terms of both the residual sum of squares and an information criterion (AIC). However, very little difference between the two could be seen by eye when the results were drawn on graph paper. In the case of the amoxicillin data, the model-independent equation was statistically superior to the double-exponential one. The applicability of this model-independent method to pharmacokinetic analysis was thus confirmed.

Keywords——pharmacokinetics; model-independent method; statistical study; curve fitting; triple-exponential decay; double-exponential decay

In our previous paper,[1] a model-independent method was proposed to describe the blood disappearance profile of intravenously (*i.v.*) administered drugs. In addition, the usefulness of this method was tested using the pharmacokinetic data for warfarin. By using roughly estimated values of four model-independent pharmacokinetic parameters (*i.e.* V_1=initial volume of distribution, K_d=distribution constant, $(V_2)_{max}$=maximum value of the additional distribution volume, and K=first-order elimination rate constant), plasma warfarin levels were calculated. Inspection showed that the calculated plasma warfarin concentrations were well fitted to the observed values.

Therefore, in this paper, a statistical study (*i.e.* curve fitting) was carried out with respect to the pharmacokinetic data for warfarin and amoxicillin using a digital computer, and the goodness of fit of this model-independent method was compared with that of the conventional pharmacokinetic analysis (*i.e.* exponential curve fitting).

Methods

Curve Fitting Procedures——Curve fitting was carried out using the SALS (statistical analysis with least-squares fitting) program[2] at Kyoto University Data Processing Center. This program has two methods for nonlinear curve fitting, namely the Gauss–Newton method with a damping option and the Levenberg–Marquardt method with Fletcher's algorithm.[3] In this study, the latter method was used. The equations used for curve fitting are as follows:

$$C = \frac{\text{Dose}}{V_1 + \dfrac{(V_2)_{max} \cdot t}{K_d + t}} e^{-Kt} \qquad (1)$$

where C is the plasma or serum drug concentration, t is the time after the *i.v.* dose, and the other parameters are explained in the introductory remarks. In addition,

$$C = P_e^{-Kt} + A_e^{-\alpha t} + B_e^{-\beta t} \qquad (2)$$

As this exponential function is a well-known one in pharmacokinetics, detailed explanation is unnecessary. When the plasma or serum concentration declined bi-exponentially, however, two exponential terms, $A_e^{-\alpha t} + B_e^{-\beta t}$, were used.

As equation 1 is not linear in terms of the parameters and derivatives are difficult to specify, the derivative free version of the SALS program was used for least-squares curve fittings.

The initial values of the parameters for the least-squares curve fittings were determined by hand calculation. The value of V_1 was calculated by dividing the injected dose by the initial concentration, and the sum of V_1 and $(V_2)_{max}$ was also calculated by extrapolation of the blood concentration *vs.* time curve at the steady state to zero time. By subtracting the value of V_1 from this sum, the value of $(V_2)_{max}$ can be obtained. To determine the value of K_d, Eq. 1 was rearranged to the following form:

$$K_d = \frac{[(V_1+(V_2)_{max})\cdot C - X_0\cdot e^{-kt}]t}{X_0\cdot e^{-kt} - V_1\cdot C} \tag{3}$$

As the value of the first-order elimination rate constant k is obtained from the terminal slope of the blood concentration *vs.* time curve, the value of K_d can be calculated by substituting the observed concentration C at time t during the distribution phase into Eq. 3. When several data points are obtained at the distribution phase, K_d value can be calculated from each data point. By determining the mean of K_ds, the accuracy of the value was increased.

Results and Discussion

Curve Fitting to the Pharmacokinetic Data for Warfarin

A triple-exponential equation, Eq. 2, was fitted to the plasma disappearance curve of warfarin by Levy *et al.*,[4,5] and the converged values of the six parameters. P, A, B, π, α, and β were determined. However, the model-independent equation, Eq. 1, has only four parameters, V_1, $(V_2)_{max}$, K_d and k. Therefore, the applicability of Eq. 1 to the pharmacokinetic data for warfarin was statistically studied. First of all, Eq. 2 was fitted to those data (unweighted, weighting function=1.0) by using the SALS program. An excellent result was obtained, as shown in Fig. 1, where the solid line represents the best-fit curve to the observed plasma warfarin concentrations. The converged pharmacokinetic parameter values are shown in Table I, which also gives two statistical parameters, the residual sum of squares (RSSQ) and an information criterion (AIC) proposed by Akaike.[6-9] Eq. 1 was fitted to the same data and a

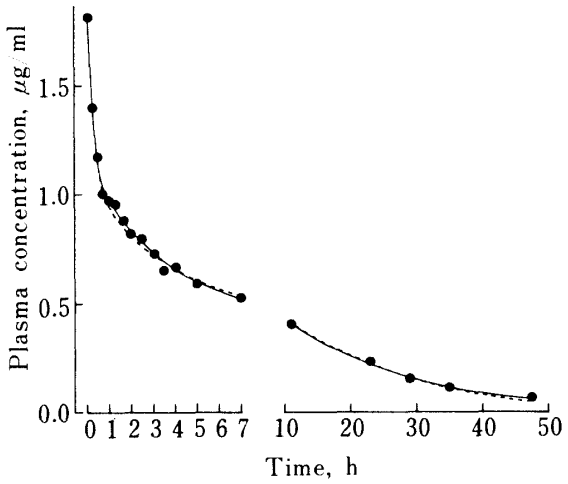

Fig. 1. Results of Nonlinear Least-squares Fitting of Plasma Warfarin Data with Equations 1 and 2

For convenience, the time scale from 0 to 7 h is expanded.
—— triple-exponential equation (Eq. 2).
····· model-independent equation (Eq. 1).

Table I. Converged Pharmacokinetic Parameters of Warfarin obtained by Nonlinear Regression Analysis

Model-independent equation	Triple-exponential equation
$V_1=40.8$ ml	$P=0.979$ μg/ml
$(V_2)_{max}=77.1$ ml	$A=0.479$ μg/ml
	$B=0.705$ μg/ml
$K_d=0.631$ h	$\pi=5.00$ h^{-1}
$k=0.0568$ h^{-1}	$\alpha=0.451$ h^{-1}
	$\beta=0.0503$ h^{-1}
RSSQ[a] $=0.0123$	RSSQ[a] $=0.0057$
AIC[b] $=-75.5$	AIC[b] $=-86.2$

a) Residual sum of squares.
b) An information criterion proposed by Akaike.[6-9]

good fitting was obtained as shown in Fig. 1 (dotted line) by nonlinear regression analysis. Statistically, Eq. 2 is superior to Eq. 1 to describe the plasma disappearance profile of warfarin. However, visually, the difference of fit between the two equations seems minor in the early period of drug distribution, namely the time period from 1 to 3 h (Fig. 1). On this basis, we consider that Eq. 1 is also applicable for the pharmacokinetic analysis of warfarin data.

Effect of Decreased Number of Data Points

As the data used in the preceding study were obtained from a basic pharmacokinetic study of warfarin,[5] there are many observed data points at the distribution phase. However, in a clinical situation, it is difficult to take many blood specimens and the number is usually less than ten. Therefore, a further study was carried out with a smaller number of observed data points at the distribution phase. As shown in Fig. 1, the terminal log-linear phase has only 5 data points. If the number of data points at the terminal log-linear phase is thus

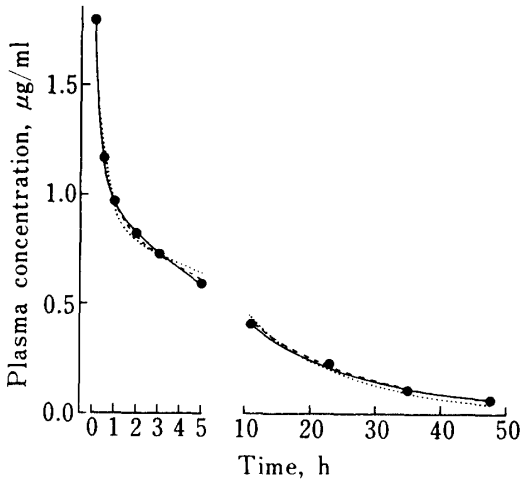

Fig. 2. Effect of Decreased Number of Data Points on the Least-squares Fitting of Plasma Warfarin Data with Equations 1 and 2

For convenience, the time scale from 0 to 5 h is expanded.
——— triple-exponential equation (Eq. 2).
- - - - - - model-independent equation (Eq. 1).
····· double-exponential equation (Eq. 2).

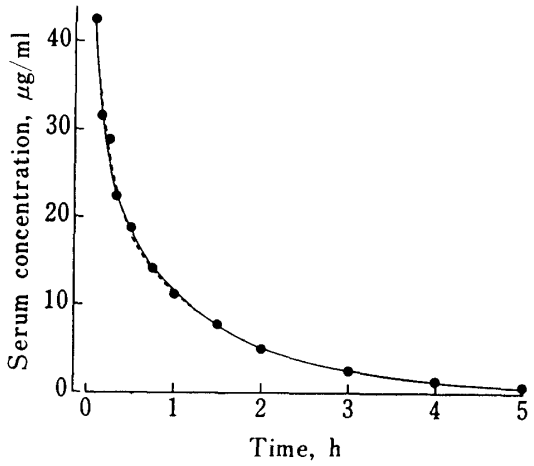

Fig. 3. Results of Nonlinear Least-squares Fitting of Serum Amoxicillin Data with Equations 1 and 2

——— model-independent equation (Eq. 1).
- - - - - - double-exponential equation (Eq. 2).

TABLE II. Converged Pharmacokinetic Parameters of Warfarin obtained by Nonlinear Regression Analysis with Fewer Data Points

Model-independent equation	Triple-exponential equation	Double-exponential equation
$V_1=41.4$ ml	$P=0.958$ μg/ml	$A=1.13$ μg/ml
$(V_2)_{max}=82.2$ ml	$A=0.439$ μg/ml	$B=0.879$ μg/ml
	$B=0.699$ μg/ml	
$K_d=0.747$ h	$\pi=3.95$ h^{-1}	$\alpha=2.35$ h^{-1}
$k=0.053$ h^{-1}	$\alpha=0.421$ h^{-1}	$\beta=0.0628$ h^{-1}
	$\beta=0.0508$ h^{-1}	
RSSQ[a] $=0.00174$	RSSQ[a] $=0.000477$	RSSQ[a] $=0.00902$
AIC[b] $=-55.5$	AIC[b] $=-64.5$	AIC[b] $=-39.1$

a) Residual sum of squares.
b) An information criterion proposed by Akaike.[6-9]

Table III. Converged Pharmacokinetic Parameters of Amoxicillin obtained by Nonlinear Regression Analysis

Model-independent equation	Double-exponential equation
$V_1=5.24$ l	$A=31.9$ μg/ml
$(V_2)_{max}=18.3$ l	$B=23.2$ μg/ml
$K_d=0.180$ h	$\alpha=5.54$ h^{-1}
$k=0.753$ h^{-1}	$\beta=0.737$ h^{-1}
RSSQ[a] $=4.14$	RSSQ[a] $=7.21$
AIC[b] $=25.0$	AIC[b] $=31.7$

a) Residual sum of squares.
b) An information criterion proposed by Akaike.[6-9]

decreased, it becomes difficult to carry out a computer curve fitting. Therefore, the data points at the distribution phase were mainly taken off. Even though the number of data pounts at the distribution phase was decreased, good curve fittings were obtained (Fig. 2). However, the double-exponential equation was not as good as the other equations to represent the plasma disappearance profile of warfarin. In terms of the values of RSSQ and AIC (Table II), Eq. 2 is superior to Eq. 1. However, the difference between the AIC values of Eqs. 1 and 2 is less than between Eq. 1 and the double-exponential equation.

On the other hand, by comparing the converged parameter values (Tables I and II), it seems that the effect of the decreased number of data points appears predominantly on the values of both K_d and $(V_2)_{max}$, which represent the drug distribution characteristics. Namely, both values were increased by about one-tenth as compared to the control values (Table I).

Curve Fitting to the Pharmacokinetic Data for Amoxicillin

In the paper of Arancibia *et al.*,[10] the mean serum concentration data from nine healthy subjects *vs.* time were analyzed with a two-compartment open model. The applicability of this model-independent pharmacokinetic analysis to their amoxicillin data was tested. Fig. 3 shows the result of curve fitting with Eqs. 1 and 2. With both equations, good fittings were obtained. However, from the values of RSSQ and AIC (Table III), Eq. 1 is superior to Eq. 2 for the purpose of describing the serum amoxicillin concentration *vs.* time curve.

Thus the applicability of the model-independent method to the pharmacokinetic analysis of warfarin and amoxicillin was confirmed in this statistical study.

References and Notes

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