Journal of Pharmacokinetics and Pharmacodynamics, Vol. 28, No. 5, October 2001 (© 2001)

A Stochastic Model Describes the Heterogeneous Pharmacokinetics of Cyclosporin

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Received November 6, 2000—Accepted July 13, 2001

The pharmacokinetics of cyclosporin (CsA) are unusual because of several heterogeneous features which include the presence of more than one conformer, considerable accumulation in erythrocytes and lipoproteins, extensive plasma protein binding, distribution into deep tissues, biliary secretion and hepatic clearance involving a large number of metabolites. In this study, a stochastic compartmental model was developed to describe the heterogeneous elimination kinetics of CsA. This new approach relies on a probabilistic transfer model with a gamma distributed probability intensity coefficient for drug elimination. For comparative purposes both the stochastic model and compartmental deterministic models were fitted to real post infusion data from patients receiving CsA as a 2-hr intravenous infusion. The criteria for selecting the best model showed that the stochastic model, although simpler than the compartmental deterministic models, is more flexible and gives a better fit to the kinetic data of CsA than the compartmental deterministic models. The stochastic model with a random rate intensity coefficient adequately describes the heterogeneous pharmacokinetics of CsA.

KEY WORDS: stochastic modeling; pharmacokinetics; cyclosporin; heterogeneity.

INTRODUCTION

Cyclosporin A (CsA), a cyclic polypeptide of fungal origin, has been widely used for the last 20 years as a potent immunosuppressive agent (1). The drug is indicated for the prophylaxis of organ rejection in allogenic transplants and for the treatment of some autoimmune diseases (2). Unfortunately, there are difficulties associated with the use of a therapeutic concentration range for routine therapeutic monitoring because CsA induces renal dysfunction and to a lesser extent hepatic toxicity (3).

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1567-567X/01/1000-0445$19.50/0

The purpose of pharmacokinetic (PK) modeling is to describe, predict and in some circumstances understand the fate of drugs in the body. Mathematical models are used to describe the administration, distribution, metabolism, and elimination processes of drugs in the organism (4). The model is identified through the time-concentration data observed and it supplies estimates of the PK parameters in a given mathematical structure. It is crucial to reliably describe the time-concentration data that yield accurate PK parameters to optimize pharmacotherapy by computing the optimal dosage regimen.

Deterministic compartmental models are generally used to describe the time-concentration data of CsA. These models are based on the concept of homogeneous well-stirred compartments in which the drug is considered to be uniformly distributed. The most suitable model seems to be a three-compartment model (5–7) but it remains inaccurate with regard to the slowest elimination phase. To date, none of these models is commonly accepted because they lack predictive power in several clinical applications.

Our experimental findings indicate that CsA PKs do not follow exponential decay described with linear compartmental modeling. Indeed, a linear relationship was found when time-post-infusion concentration CsA data were plotted on log–log axes. Linear log–log plots are indicative of power-of-time laws which usually arise from fractal processes (8). Wise (9) has used power functions of time as alternatives to the sum of exponentials models and he has validated these approaches on many sets of data. Like other researchers (10) in the field of kinetic data analysis, Wise criticized the notion of "homogeneous compartment" and used "power-of-time" models without the hypothesis of homogeneous distribution. On the other hand, stochastic compartmental models have been applied extensively (11–14) in many fields of research, and "power-law" models, similar to "power-of-time" models, have been derived to describe non-homogeneous processes.

The reasons for using stochastic models in PKs are mainly the non-instant mixing and the compartment heterogeneity. Non-instant mixing is a physiologically-sound concept not only for solutes distributed extravascularly but also for the solutes confined in the intravascular space (15). Non-homogeneous compartments, on the other hand, are a natural consequence of the lumping inherent in the division of the body into two, three, or more compartments. These heterogeneous characteristics of the human body, both in structure and function, in conjunction with the complicated PKs of CsA and our experimental observations, prompted us to develop stochastic compartmental models for describing the heterogeneous nature of the CsA elimination process. The new model established herein is sufficiently flexible to fit the available time-concentration CsA data and it opens new perspectives in PK modeling.

THE REAL DATA

CsA was given intravenously to 52 patients aged 17–47 years (5). Each patient received a 2-hr infusion of CsA ($4\,mg\,kg^{-1}$) with constant infusion rate, 15 days before allogenic bone marrow graft. Blood samples were collected just before the end of infusion and then at 5, 10, 20, and 30 min and 1, 2, 3, 6, and 12 hr after the end of the infusion. The concentration levels were measured by HPLC (16). Here, we have $m = 10$ time-concentration pairs (t_i, y_i), $i = 1, \ldots, m$ per patient.

METHODS

Probabilistic Transfer Models

Stochastic compartmental models assume that, at the molecular level, the process can be described only in terms of a probability that a molecule will enter or exit the compartment at any time. These models are called *probabilistic transfer* models and involve the probability intensity coefficients instead of the deterministic transfer rate constants (14). *Probabilistic transfer* models are expressed by the Chapman–Kolmogorov differential equations of the compartmental structure.

Random Rate Stochastic Models

Random rate stochastic models are extensions of *probabilistic transfer* models in which the heterogeneity of molecules is introduced through random probability intensity coefficients. The molecules are assumed to differ in their passage probabilities because of inherent variability in such characteristics as molecular weight, conformations, or chemical composition. The random variable is the probability intensity coefficient, which is distributed according to a given probability density function (pdf).

Stochastic Modeling of CsA

Using the methodology of Matis (17), we considered the single compartment case, where the drug amount D is given over a period T by a constant rate infusion and data are available only after the end of infusion.

(1) The Probabilistic Transfer Model

For the above experimental context, the *probabilistic transfer* model predicts the probability of a CsA molecule being in the compartment at

time $t\,(T < t)$:

$$p(t,k) = \frac{1}{Tk}[e^{-k(t-T)} - e^{-kt}] \tag{1}$$

where k is the elimination probability intensity coefficient. Full details are given in the Appendix.

(2) The Stochastic CsA Elimination

Let us assume that k is a random variable regarding molecules. Several pdfs can be used to express the statistical variability of k, leading to several stochastic one-compartment models. The distribution used here is the gamma distribution, $k \sim \gamma(k; a, b)$ (18) with positive a and b, the shape and scale parameters, respectively. The resulting probability transfer model is this mixture:

$$\begin{aligned} p(t) &= \int_k p(t,k)\gamma(k;a,b)\,dk \\ &= \frac{1}{T(a-1)b}\{[1+b(t-T)]^{-(a-1)} - (1+bt)^{-(a-1)}\} \end{aligned} \tag{2}$$

The pdf of CsA Molecules

Because of the independence of the n molecules contained in the infused amount D, the number of drug molecules $n(t)$ present in the compartment at time t follows the $n(t) \sim B[n(t); n, p(t)]$ binomial distribution, with expectation and variance equal to $np(t)$ and $np(t)[1-p(t)]$, respectively.

(4) The Stochastic Characteristics of CsA Concentration

Given the gram-molecular weight of the drug and using Avogadro's number, one converts the number of molecules n and $n(t)$ to the equivalent amounts D and $q(t)$, respectively. Assuming a constant volume of distribution V and dividing $q(t)$ by V, one obtains the expectation $E[y(t)]$ and variance $\mathrm{Var}[y(t)]$ of the drug concentration $y(t)$ at time t. Its expectation and variance are:

$$E[y(t)] = \frac{D}{V}p(t) \quad \text{and} \quad \mathrm{Var}[y(t)] = \frac{D^2}{nV^2}p(t)[1-p(t)] \tag{3}$$

respectively. From these relations, the coefficient of variation CV is:

$$CV = \frac{\sqrt{V[q(t)]}}{E[q(t)]} = \sqrt{\frac{1}{n}\frac{1-p(t)}{p(t)}}$$

CV is not a small number only for drugs administered at very low doses; otherwise, $CV \ll 1$ as in PKs (19,20). From a mechanistic point of view, if the number of molecules present is not large, the concentration as function of time will show the random fluctuations we expect from chance occurrences. However, if the number is very large as in PKs, these fluctuations will be negligible and, for purposes of estimation, the stochastic error may be omitted in comparison with the measurement error.

It is important to note that, in the general case, the stochastic errors have slight serial correlation and hence are not independent. In the PK context, since only the measurement error is taken into account, the analysis is unaffected by the time-wise dependency.

The one-compartment stochastic model leads to a "power-law" expression involving 3 parameters V, a, and b. Clinical relevant parameters can be derived from V, a, and b. For example, the stochastic clearance CL_S can be derived as:

$$CL_S = \frac{D}{\int_0^\infty E[y(t)]\,dt} = Vb|a-1|$$

Deterministic Models

For comparative purposes, we used 2- and 3-compartment deterministic models with 4 and 6 parameters, respectively:

$$y(t) = \frac{D}{T}\sum_{i=1}^{N}\frac{A_i}{a_i}[e^{a_i - 1_i(t-T)} - e^{a_i - 1_i t}] \tag{4}$$

where N is the number of compartments. From the estimates for A_i and a_i, relevant PK parameters can be computed, e.g., the deterministic clearance CL_D, the volume of distribution of the central compartment V_1, etc.

Data Fitting and Parameter Estimation

Since the stochastic error is negligible in comparison with the measurement error e_i, the discrepancy $y_i - E[y(t_i)]$ between observation and prediction is attributed only to e_i. Measurement errors are assumed to be independent and normally distributed, with zero mean and heteroscedastic variance, i.e., $\mathrm{Var}[e_i] = K^2E^2[y(t_i)]$, where K is the coefficient of variation of the measurement error.

All models and complementary techniques were programmed within MATLAB (21). Fitting and parameter estimation were done by BFGS (22), a quasi-Newton algorithm maximizing the likelihood function (23). In all these nonlinear models, parameters can be unidentifiable because of the

redundancy of parameters in the model structure. A consequence is ill-conditioned confidence contours in the parameter space (23). Ill-conditioning may be determined by examining the eigenvalues $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_p$ of the Fisher information matrix: the condition number (cn), defined as $cn = \lambda_1/\lambda_p$, measures the parameter redundancy. In practice, the parameter redundancy also leads to abnormally high or low estimates of model parameters.

For each model, the CsA time-concentration profiles were evaluated in terms of the estimated model parameters. Among the well-conditioned estimates, the best model was selected by means of Akaike Information Criterion (AIC) (24). The root mean squared error (RMSE) was also reported to compare the goodness of fit of the models used.

RESULTS

Figure 1 is a log–log plot of the observed time-concentration data normalized by the total administered amount for the 52 patients. After a quick decline of concentrations just at the end of infusion, all data seem to follow a linear decrease, suggesting a "power-of-time" model. Inspection of Eq. (2) reveals that for t close to T, the model is actually the difference of two "power-law" terms explaining the quick decline of concentration just after the end of infusion, Fig. 1. For $t \gg T$, the model produces a "power-of-time" behavior.

The cn and RMSE over the 52 kinetic profiles were represented by smoothed histograms (25). Relative to the mean, the histogram better describes the model performances over all the kinetic profiles.

Parameter Redundancy

For the three models, Fig. 2A illustrates the histogram of log(cn). The 3-compartment deterministic model shows higher log(cn) values, and it is presumed to be parameter redundant. Indeed, this model causes convergence problems and 28 data sets led to unreliable estimates. In contrast, the stochastic model gives the lowest log(cn) values; it is the best conditioned. Even with this model, redundancy is observed for 5 data sets: these data could be described by a model even simpler than the stochastic one. The 2-compartment model is an intermediate case between the previous ones. Consequently, the 3-compartment model was excluded for subsequent analysis and the stochastic and the 2-compartment models were further compared.

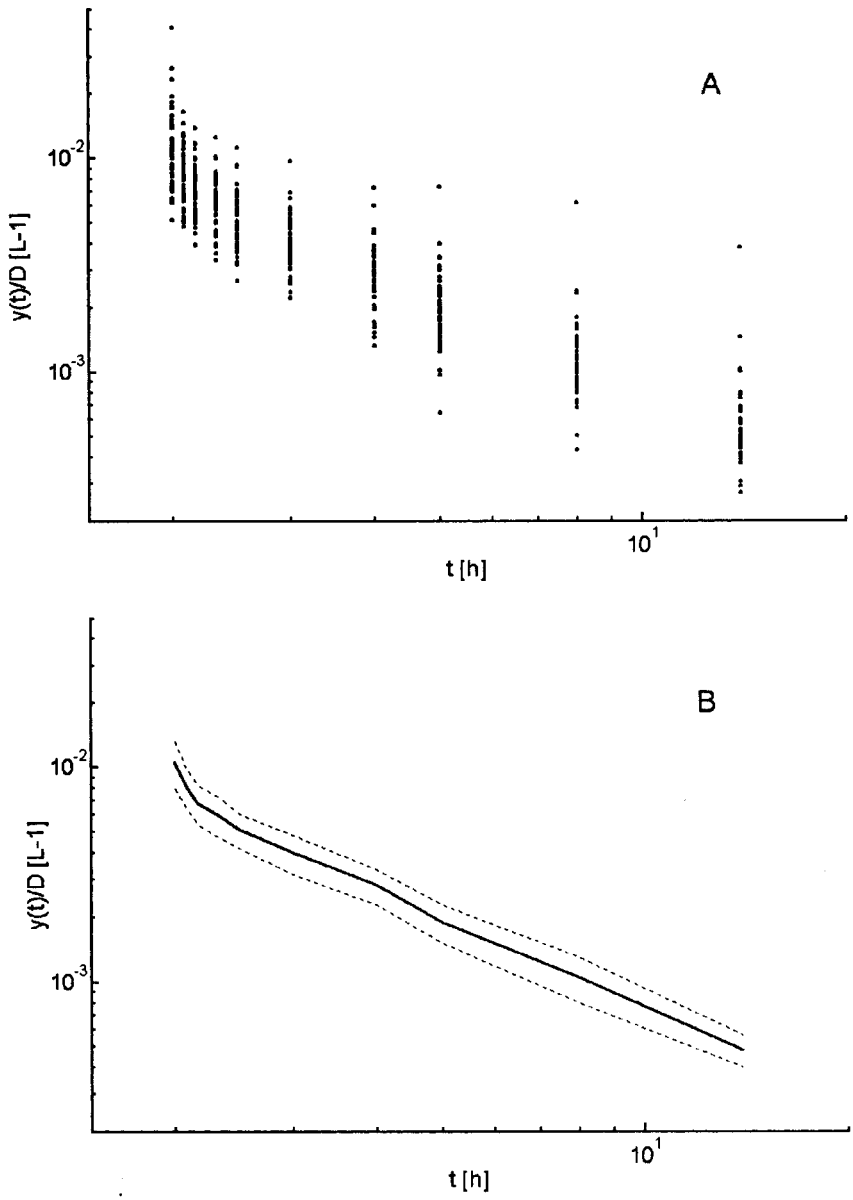

Fig. 1. The time-concentration curves reduced to the doses. Raw data on the 52 patients (A) and median curve with interquartile range (B).

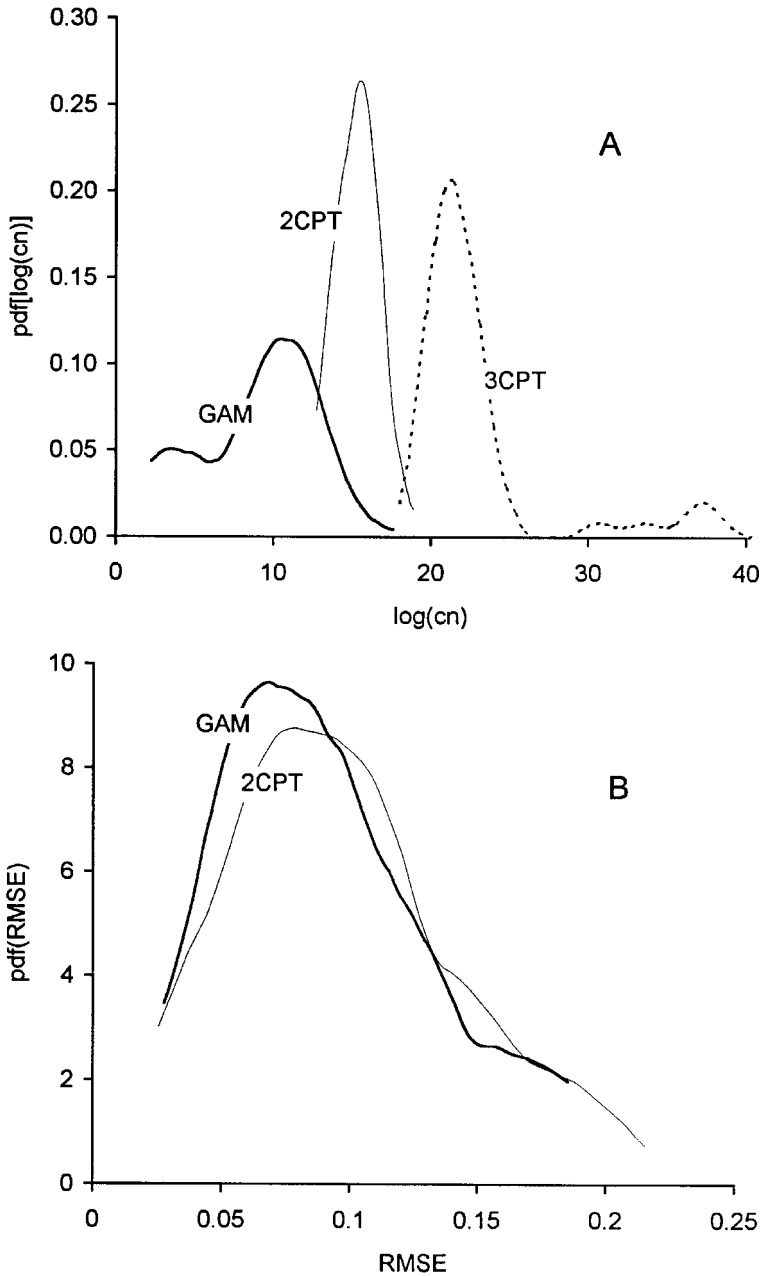

Fig. 2. Smoothed histograms for log(*cn*) (A) and RMSE (B). GAM: stochastic model, 2CPT: two compartment model, 3CPT: three compartment model.

The Best Model Selection

Given the number of model parameters, AIC compares the adequacy of models on data. The goal of AIC is to discriminate among fitted models with a different number of parameters. The rule of parsimony tends to select models with lower numbers of parameters having an acceptable fitting. Values of AIC for the stochastic model were lower than those for the 2-compartment deterministic model in 38 out of 52 cases (Fig. 2B). Thus, the stochastic model fits the CsA data better than does the 2-compartment deterministic model. The median of RMSE and the associated interquartile range were 8.28 and 5.29% for the stochastic model and, 9.19 and 6.09% for the deterministic model. Figure 3 shows the best, the median, and the worst fitted data with the stochastic model.

Dispersion of the Model Parameters

After removing the 5 data sets leading to parameter redundancy in the stochastic model, we determined the median values, interquartile ranges and indices of skewness for V, a, and b estimates, and for the computed CL_S, CL_D, and V_1 parameters (Table I). For the median values of a and b, Fig. 4 represents the γ pdf of the random probability intensity coefficient k. The first two moments of this pdf are:

$$E_\gamma = a \cdot b = 3.638\ \text{hr}^{-1} \quad \text{and} \quad V_\gamma = a \cdot b^2 = 11.942\ \text{hr}^{-2}$$

Figure 5 shows the dispersion of 47 data sets. In the diagonal elements are plotted the smoothed histograms of the 3 parameters and in the lower triangular part the scatter diagrams. Dispersion for V is nearly uniform; it is normal for a and asymmetric for b. Also, weak correlations were found between these parameters.

DISCUSSION

In this study, the 3-compartment model is parameter redundant and the stochastic model, although it has one parameter less than the 2-compartment model, fits the CsA data better. The stochastic model is obtained by associating a *probabilistic transfer* model with a gamma distributed probability intensity coefficient for the drug elimination. The model established has only 3 adjustable parameters and it is flexible enough to fit the available time-concentration CsA data. In the limit as a approaches 1, the γ pdf becomes an exponential pdf and the model can be further simplified with only two adjustable parameters. Obviously, this is the case for some of CsA kinetic data sets for which parameter redundancy was observed since the

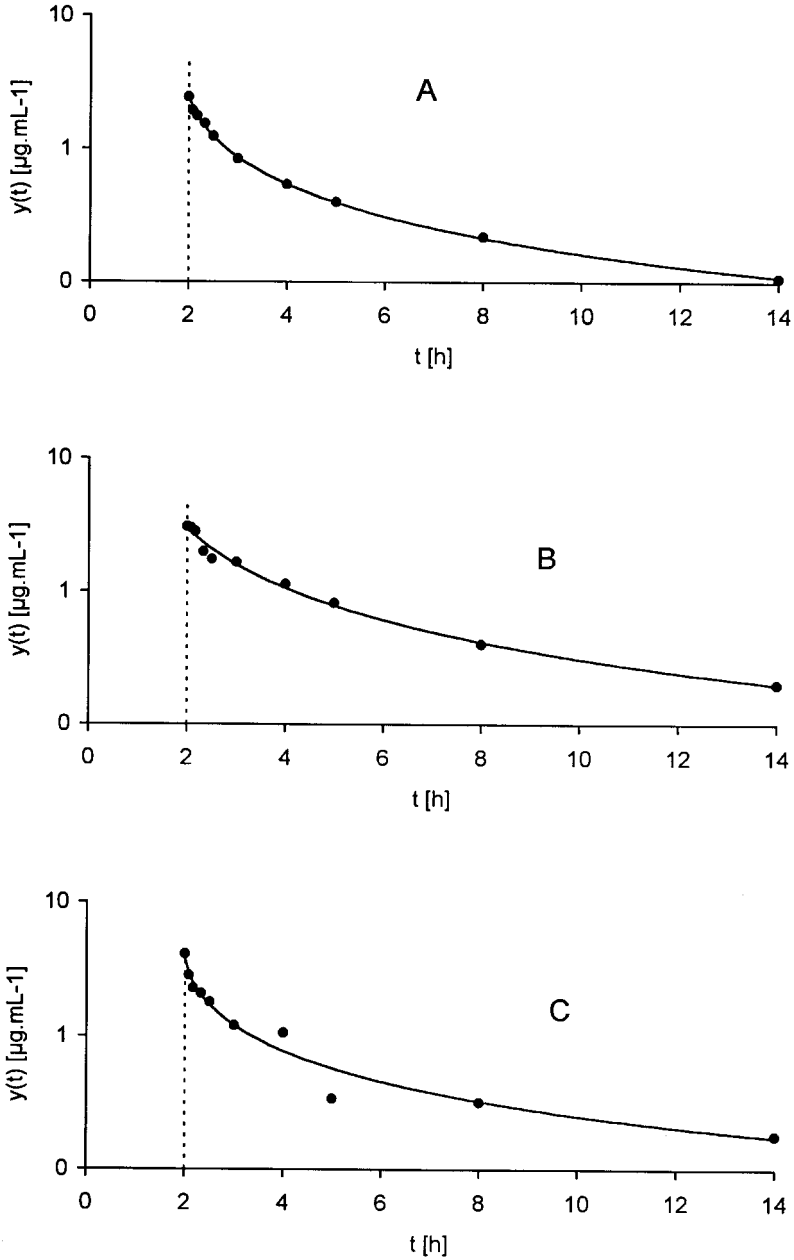

Fig. 3. The best (A), median (B), and worst (C) fit of data with the stochastic model.

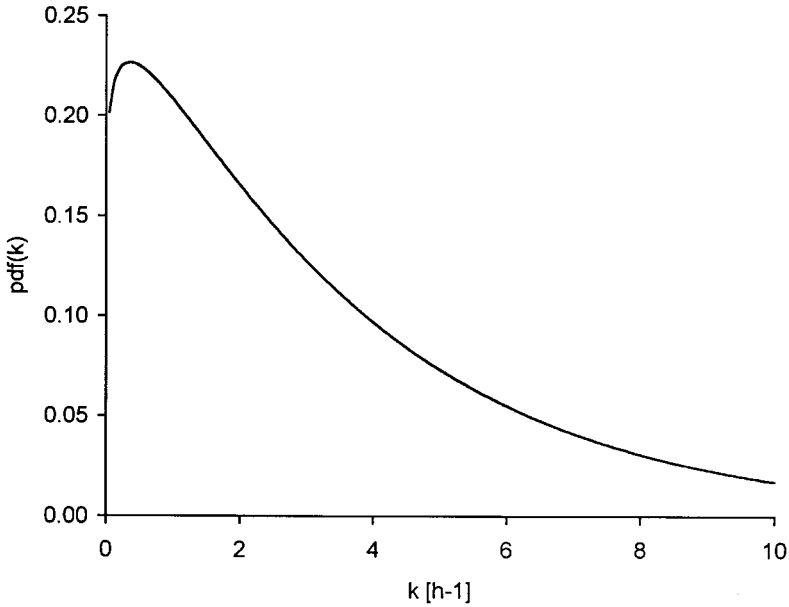

Fig. 4. For the median values of a and b, the γ pdf of the random probability intensity coefficient k.

estimate for a is close to unity, Table I. By comparing the respective parameters for the stochastic and deterministic models, it seems that V is of the same magnitude as V_1, but CL_D is twice higher than CL_S. However, the areas under the concentration–time curve for the observation interval (from 0 up to 14 hr) derived from the two models and used for the calculation of CL_D and CL_S are similar and close to the experimental value calculated using the log trapezoidal rule (median value $0.0350\,\mathrm{hr\,L^{-1}}$ for the areas reduced to the administered dose). This result indicates that the difference between CL_D and CL_S is most likely associated with the calculations of the extrapolated areas from the end of the observational interval to infinity. Indeed, the extrapolated areas for the stochastic model were found to be much higher than the corresponding areas for the deterministic model (median values 0.0587 vs. $0.0033\,\mathrm{hr\,L^{-1}}$). Thus, given the relatively short observational period in this study, CL_D is rather overestimated while CL_S is highly influenced by the extreme values of the scale parameter b (large interquartile range with respect to the median value, 4.499 vs. $3.283\,\mathrm{hr^{-1}}$). Although a longer observation interval would improve the clearance estimates, the reported in the literature CsA clearance values obtained by non-compartmental analysis of steady-state data using either long-term infusions

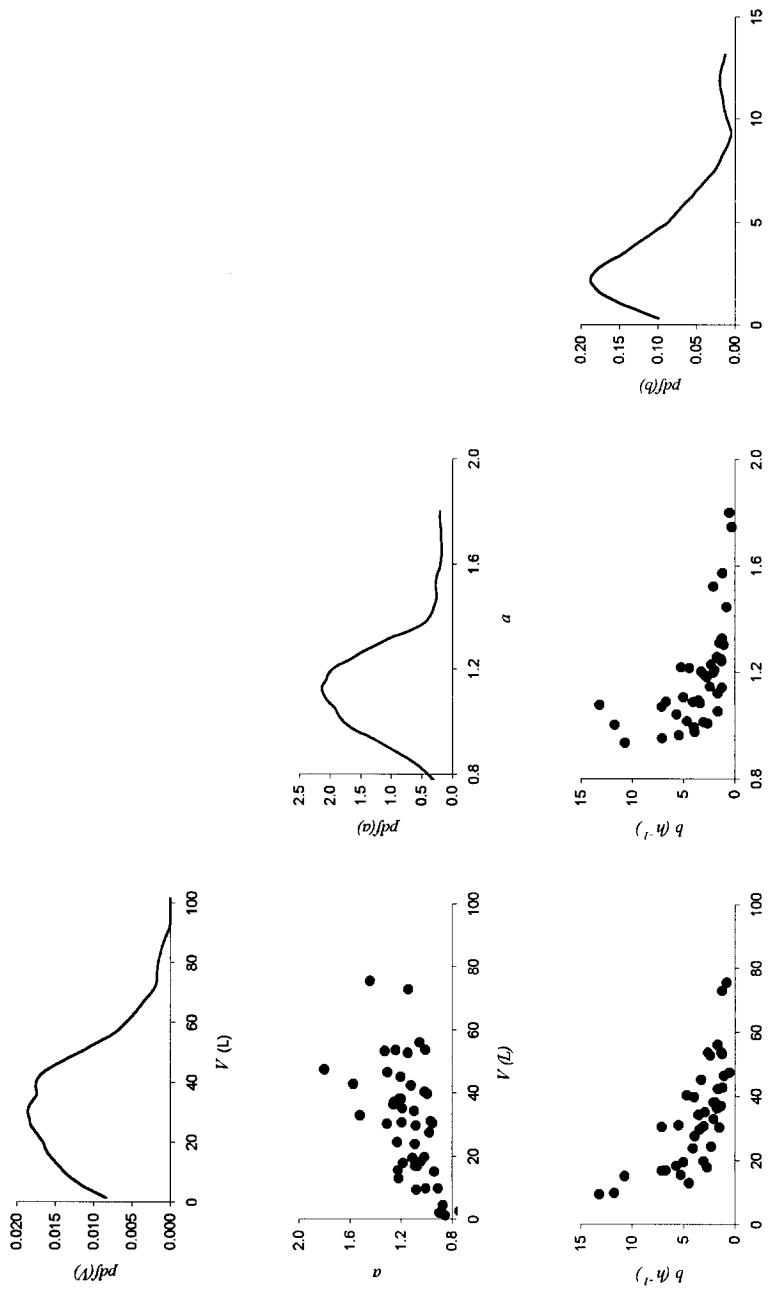

Fig. 5. The dispersion of 47 data sets. In the diagonal elements are plotted the smoothed histograms for V, a and b and in the lower triangular part, the scatter diagrams.

Table I. Statistical Summary of the Estimated Parameters for the Stochastic and Deterministic Model

	Stochastic model				2-cpt deterministic model	
	V (L)	a	b (h^{-1})	CL_S (L hr^{-1})	V_1 (L)	CL_D (L hr^{-1})
median	30.83	1.108	3.283	13.06	36.12	28.49
iqr	25.72	0.219	4.499	12.27	26.94	9.84
iskew	1.813	0.437	3.21	6.47	1.663	–0.310

iqr: interquartile range; iskew: index of skewness.

(26) or multiple oral administration (27) (assuming an average bioavailability of 0.3 for Sandimmune® (28)) lie between the estimates for CL_S and CL_D found in this study.

In compartmental analysis, it is common practice to fit the kinetic data by a sum of exponentials and then postulate that the number of compartments in the system is at least as large as the number of exponential terms required to achieve an acceptable fitting. This practice, however, is inappropriate and may be very misleading when a random elimination rate coefficient, k, is present. Indeed, a stochastic one-compartment model with k having two possible outcomes behaves like a biexponential function. When the number of outcomes of k becomes high, the sum of exponentials is reduced to a "power-of-time" function. For this reason, Matis (29) emphasized that one cannot imply on the basis of observed data alone that a multiexponential fitting is sufficient evidence of a multicompartmental system.

Due to the small number of its parameters, the developed stochastic model could be used for population analyses. Covariates can be readily incorporated into this model to explain the interindividual variability of parameters. Needless to say, that this model can be also used for simulation and dosage adjustment purposes.

CONCLUSION

Several features of CsA PKs contribute towards heterogeneity in the kinetic behavior: extensive protein binding, considerable accumulation in erythrocytes and lipoproteins of free and bound forms, distribution into deep tissues, biliary secretion and hepatic clearance involving a large number of metabolites. Thus, the CsA molecules can differ in their kinetic behavior because of inherent variability in such characteristics. Moreover, CsA is a cyclic peptide of eleven residues with several backbone conformations which may exhibit different biotransformation rates contributing towards the random character of the elimination process. These heterogeneous features prompted us to develop a stochastic model in order to empirically describe the observed time-concentration CsA data. Our model

can be considered as an alternative to the physiologically based pharmacokinetic models (30,31). In the latter, heterogeneity in kinetic behavior is implemented by representing the body as a series of compartments, each with physiological blood flow, volume and tissue partition coefficient. Although the stochastic model does not explain the source of heterogeneity, it is flexible enough to provide reliable estimates for PK parameters of common clinical data.

The term "compartment" was introduced in compartmental analysis to define a kinetically homogeneous amount of material (32). In PKs, the concept of "homogeneous compartment" was used in order to simplify the prototype system and make the mathematical analysis feasible. Later on, due to the complexity and the diversity of observed data, more complex multicompartmental models were developed. Again, homogeneity in the drug concentration for each one of the compartments of the model is the prevailing concept. Today, there are alternative approaches to the analysis of complex phenomena. For example, one can describe the heterogeneous character of the processes in the body using the compartmental notion in conjunction with statistical tools (stochastic approaches). This is accomplished by considering heterogeneity in the compartments, which is a more realistic concept. Our approach relies on the so-called "heterogeneous compartment" in an attempt to represent a set of more complex structures with numerous underlying compartments. This approach is against the unrealistic notion of the "well-stirred" system and is simpler mathematically than homogeneous multicompartment models. At first glance, this seems to be a paradox since the conventional approaches rely on a simpler hypothesis, i.e., homogeneity. Plausibly, this paradox arises from the analytical power of stochastic approaches.

Our more realistic model is in agreement with recent observations supporting the heterogeneous character of drug processes in the human body (33–36). The common denominator of these studies is the realization that the non-homogeneous understirred spaces affect the drug diffusion characteristics and produce deviations from the classic behavior. In this context, Weiss challenged the concept of the homogeneous volume of distribution for amiodarone and proposed a more physiologically-based model using fractal description of drug kinetics and a time-varying volume of distribution inside a biological space (35).

It is clear that the "power-law" models developed here differ from the "power-of-time" models both in their justification and in their mathematical form. However, the two concepts are relevant since the γ pdf belongs to the family of Weibull distribution which has been used to describe fractal processes obeying "power-of-time" laws (37). Stochastic modeling with random rate coefficients is a rich theoretical tool for describing complex kinetic data

and stochastic models may be regarded as a broad class of alternatives to the exponential decay model (38). The stochastic model has proved simpler and more flexible than the classic deterministic models for CsA PKs and we encourage its use for performing more realistic and reliable PK studies with other drugs.

APPENDIX: THE PROBABILISTIC TRANSFER MODEL

We developed a probabilistic transfer model that includes one compartment for drug distribution and is associated with a constant rate infusion. In Fig. 6, indices 1 and 2 denote the infusion balloon and the single compartment of distribution, respectively.

The parameters h and k in the model are the probability intensity coefficients. They are defined through the conditional probability that any random molecule present at time t leaves a compartment by $t + \Delta t$:

$$\Pr\{\text{leave 1 by } t + \Delta t / \text{present in 1 at } t\} \equiv h\,\Delta t$$

and

$$\Pr\{\text{leave 2 by } t + \Delta t / \text{present in 2 at } t\} \equiv k\,\Delta t$$

for small Δt.

Probability Intensity Coefficient for the Constant Rate Infusion

The leaving process from the infusion balloon with constant rate is given by:

$$\Pr\{\text{leave 1 before } t\} = \begin{cases} t/T & t \le T \\ 1 & T < t \end{cases}$$

and

$$\begin{aligned} h\,\Delta t &\equiv \Pr\{\text{leave 1 by } t + \Delta t / \text{present in 1 at } t\} \\ &= \frac{\Pr\{\text{present in 1 at } t, \text{ leave 1 by } t + \Delta t\}}{\Pr\{\text{present in 1 at } t\}} \end{aligned}$$

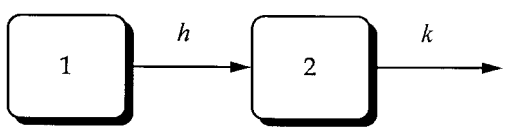

Fig. 6. Compartmental model for CsA administration by infusion.

where Pr{present in 1 at t, leave 1 by $t+\Delta t$} is the joint probability that a molecule is present in 1 at t and leaves by $t+\Delta t$; it is equal to Pr{leave 1 before $t+\Delta t$} − Pr{leave 1 before t}. Also, Pr{present in 1 at t} = 1 − Pr{leave 1 before t} and the previous definition becomes:

$$h = \frac{1}{T-t}[u(t) - u(t-T)] \tag{A1}$$

where $u(t)$ is the Heaviside step function.

Chapman–Kolmogorof Equations for the System

(1) Let $p_{11}(t)$ be the probability that a particular molecule introduced at time 0 in 1 is still in 1 at time t. The necessary events for a molecule to be present in 1 at time $t+\Delta t$ are:

$$\Pr\{\text{present in 1 at } t+\Delta t\} = \Pr\{\text{present in 1 at } t\} \times \Pr\{\text{present in 1 from } t \text{ to } t+\Delta t\}$$

or

$$\Pr\{\text{present in 1 at } t+\Delta t\} = \Pr\{\text{present in 1 at } t\} \times [1 - \Pr\{\text{leave 1 by } t+\Delta t/\text{present in 1 at } t\}]$$

or using the mathematic notations:

$$p_{11}(t+\Delta t) = p_{11}(t)[1 - h\,\Delta t]$$

Rearranging and taking the limit as Δt approaches 0, one has the differential equation:

$$\frac{dp_{11}(t)}{dt} = -hp_{11}(t) \qquad p_{11}(0) = 0$$

Given Eq. A1, the analytic solution is:

$$p_{11}(t) = \begin{cases} (T-t)/T & t \le T \\ 0 & T < t \end{cases} \tag{A2}$$

(2) Let $p_{12}(t)$ be the probability that a particular molecule introduced at time 0 in 1 is in 2 at time t. The necessary events for a molecule to be set

in 1 at time 0 and present in 2 at $t + \Delta t$ are:

$$\begin{aligned}
&\Pr\{\text{set in 1 at 0, present in 2 at } t + \Delta t\} \\
&\quad = \Pr\{\text{set in 1 at 0, present in 1 at } t\} \\
&\qquad \times \Pr\{\text{leave 1 by } t + \Delta t / \text{present in 1 at } t\} \\
&\qquad + \Pr\{\text{set in 1 at 0, present in 2 at } t\} \\
&\qquad \times \Pr\{\text{present in 2 between } t \text{ and } t + \Delta t / \text{present in 2 at } t\}
\end{aligned}$$

or using the mathematic notations:

$$p_{12}(t + \Delta t) = p_{11}(t) h \Delta t + p_{12}(t)[1 - k \Delta t]$$

Taking the limit as Δt approaches 0, one has:

$$\frac{dp_{12}(t)}{dt} = h p_{11}(t) - k p_{12}(t) \qquad p_{12}(0) = 0 \tag{A3}$$

By reporting Eq. (A2) into Eq. (A3) and solving the so obtained differential equation:

$$p_{12}(t) = \frac{1}{Tk} \begin{cases} 1 - e^{-kt} & t \le T \\ e^{-k(t-T)} - e^{-kt} & T < t \end{cases}$$

This equation computes the probability that a molecule, set in balloon at time 0, is present in distribution compartment at time t.

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