Pharmacokinetic Variability and Therapeutic Drug Monitoring Actions at Steady State

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Purpose. To develop a mathematical model for therapeutic drug monitoring and to assess the kinetic relationships between the intensity of corrective action and the approach of drug concentrations to target values.

Methods. A mathematical model that succinctly accounts for the corrective actions and the variability inherent in the pharmacokinetics was used.

Results. The validity of the variability term was tested using experimental data for steady state concentrations of the drug procainamide. The approach of the monitored process to the target value followed exponential kinetics and an analytical expression for dependence the variance with time and various dosing parameters was derived. The variance of the drug concentration depends critically on a single nondimensional parameter containing the rate constant for the therapeutic corrective actions and a coefficient describing the variance rate. When the rate constant for the therapeutic corrective actions was less than this critical value, the variance increased indefinitely.

Conclusions. From a dosing standpoint, large variances in drug concentrations are undesirable because some patients will be overdosed or underdosed. Since deterministic models cannot provide analytical solutions for the moments of drug concentration distribution functions, stochastic models can be used to provide useful insights into the design of therapeutic regimens.

KEY WORDS: modeling; stochastic; Log-normal; distributions; pharmacodynamics.

INTRODUCTION

During steady state dosing, there is risk associated with how an individual patient will respond to a treatment because of pharmacokinetic and pharmacodynamic variabilities (1) that are stochastic in nature and can result in either treatment failure due to inadequate exposure, or toxicities due to excessive exposure.

Stochastic modeling approaches have the potential to provide insights into a variety of pharmacokinetic and pharmacodynamic problems: The use of these approaches to examine the contributions of pharmacokinetic variability to pharmacodynamic variability and to assess the risks associated with unanticipated drug interactions has been demonstrated (2,3). The goal of this paper was to examine the implications of a stochastic model for therapeutic drug monitoring.

For a drug with a given pharmacodynamic-pharmacokinetic profile, the frequency of monitoring and the intensity of corrective action are critical variables since they determine the cost-benefit ratio in therapeutic drug monitoring (4). Bayesian (and non-Bayesian) estimation has been widely used to optimize sampling times with the principal objective of improving the estimation of pharmacokinetic parameters (5,6).

The model in this report examines the impact of random variations or drift in the pharmacokinetics on therapeutic monitoring strategies. The equations are derived for steady state dosing, an assumption which is reasonable for many chronic drug treatment regimens. The model yields analytical results that allow the impact of dosing parameters to be assessed without recourse to extensive simulation.

DERIVATIONS AND RESULTS

The Stochastic Process for Steady State Dosing

We assume that in the presence and the absence of therapeutic drug monitoring, the concentrations can be described in the form of an Ito process (7):

$$dx = a(x, t)\, dt + b(x, t)dz \tag{1}$$

where $a(x, t)$ is the drift rate or trend, $b^2(x, t)$ is the variance rate, dt is differential time and dz is the differential of the Wiener variable, z.

The functions a and b in Eq. (1) are generally, functions of x and t. For example, for a drug with first-order pharmacokinetics, the concentration profile C(t) resulting from an elimination rate constant K yields an $a(x, t)$ of:

$$a(x, t) = -KC \tag{2}$$

In steady state dosing regimens, $a(x, t) = 0$. If the square root of the variance rate function, $b(x, t)$, of the drug is characterized by a constant coefficient of variation, σ, then at steady state:

$$dC = \sigma C\, dz \tag{3}$$

Using Ito's lemma, it can be shown that concentrations in such systems follow a log-normal distribution (3,8).

Validating the Predictions of the Stochastic Model for Steady State Dosing

The validity of these predictions was challenged for steady state dosing using a clinically derived data set from Koch-Weser (9) for dosing rates of 3 g/day or 2–2.25 g/day. Figure 1 is a probability plot that examines the hypothesis that the logarithms of the concentration are normally distributed. On such a plot, the points lie along a straight line when they are log-normally distributed and Fig. 1 demonstrates that the log-normal prediction is reasonable. This was confirmed using a one-sample Kolmogorov-Smirnov test to challenge the null hypothesis that the logarithms of the concentrations were normally distributed. The statistical analysis did not reject the null hypotheses (P values greater than 0.95). These results support the underlying model for variance rate in steady state dosing of procainamide.

The Stochastic Process Under Therapeutic Drug Monitoring

Assume that the care provider has established an initial steady state concentration (C_0, a constant), and wishes to

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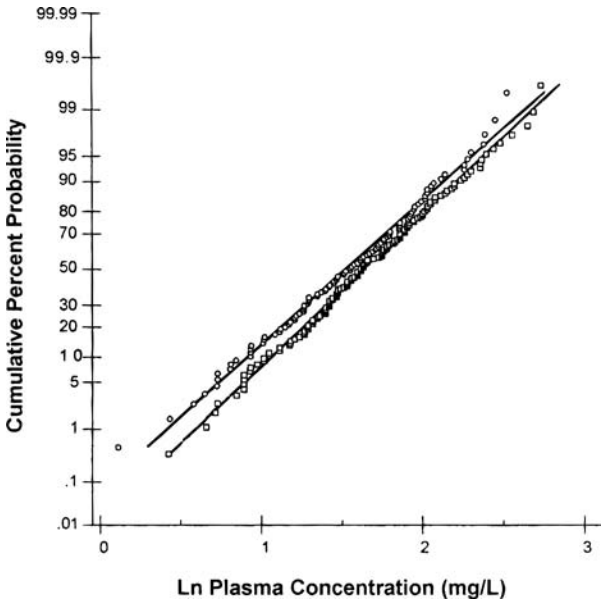

Fig. 1. The steady state concentration distribution of procainamide plotted against the cumulative percent probability. The data were extracted from the report by J. Koch-Weser (9). The open circles represent plasma concentrations at a daily dose of 2 to 2.25 g and the open squares represent the plasma concentrations at daily dose of 3 g/day. The solid line is the best fit line through the points.

achieve a target concentration C_s. To assess the impact of therapeutic drug monitoring, we assume that any deviations from a set or long term value of C_s are continuously corrected and the intensity of the correction is characterized by a term proportional to the extent of the deviation from the target concentration. The rate constant for the correction process is a constant α. The stochastic differential equation that models actual changes in drug concentration C is:

$$dC = \alpha(C_s - C)dt + \sigma C dz \tag{4}$$

The term α is a rate constant that is related to the frequency or speed of corrective action and its reciprocal represents a time scale over which the corrective measures take effect. As previously discussed, the term $\sigma C dz$ models variability. This equation is a general scalar linear stochastic equation, and the conditional mean $m(t) \equiv E[C|C_0]$, at time t is the solution to the ordinary differential equation (10):

$$\frac{dm(t)}{dt} + \alpha m(t) = \alpha C_s \tag{5}$$

Since the expected value of the concentration at time $t = 0$ is C_0, the solution is (11):

$$m(t) = C_s(1 - e^{-\alpha t}) + C_0 e^{-\alpha t} \tag{6}$$

The expectation $E[C^2|C_0] \equiv P$, is the solution to the ordinary differential equation (10,11):

$$\frac{dP(t)}{dt} + (\sigma^2 - 2\alpha)P(t) = 2\alpha C_s m(t) \tag{7}$$

with initial condition $P(0) = E[C_0^2] = C_0^2$

The variance $Var(C|C_0)$, of the concentration in the monitored process is:

$$Var[C|C_0] = e^{-(2\alpha-\sigma^2)t}\left[C_0^2 + \frac{2C_s\alpha(C_s - C_0)}{(\alpha - \sigma^2)} - \frac{2C_s^2\alpha}{(2\alpha - \sigma^2)}\right] - [(C_0 - C_s)^2 e^{-2\alpha t}] - \left[\sigma^2 e^{-\alpha t}\frac{2C_s(C_s - C_0)}{(\alpha - \sigma^2)}\right] + \left[\frac{C_s^2\,\sigma^2}{(2\alpha - \sigma^2)}\right] \tag{8}$$

Dependence of the Mean and Variance of the Concentration Distribution Function on Monitoring Parameters

The expression for the mean, Eq. (6), is consistent with the conventional pharmacokinetic intuition: i.e., for a deterministic one-compartment model with zero order infusions, the equation describing the kinetics of concentration changes has exactly the same mathematical form. For a deterministic process, the value of $\sigma = 0$ and the variance predicted by Eq. (8) is zero. Thus, the stochastic differential approach yields the deterministic result as a special case.

The constant α in a monitored process is the proportionality constant with which the caregiver converts deviations from the target concentrations into changes in the infusion rate. The results of Eq. (6) show that for a monitored therapeutic process, the target concentration C_s is achieved over the time scale α^{-1}. For example, a concentration halfway between C_0 and C_s will be achieved after a time interval equal to $(\ln 2/\alpha)$.

These expressions for mean and variance also have the following asymptotic properties:

$$\lim_{\alpha\to\infty} E[C|C_0] = C_s \tag{9}$$

$$\lim_{\alpha\to\infty} Var[C|C_0] = 0 \tag{10}$$

$$\lim_{t\to\infty} E[C|C_0] = C_s \tag{11}$$

$$\lim_{t\to\infty} Var[C|C_0] = \frac{C_s^2\sigma^2}{2\alpha - \sigma^2} \text{ for } \alpha > \frac{\sigma^2}{2} \tag{12a}$$

$$\lim_{t\to\infty} Var[C|C_0] = \infty \text{ for } \alpha \le \frac{\sigma^2}{2} \tag{12b}$$

The first two asymptotic limits are consistent with ideal control: i.e., if the drug monitoring process is extremely responsive and frequent ($\alpha \to \infty$), then the target concentration C_s will be achieved and the variance will be zero.

In the limit of long time, $t \to \infty$, the mean concentrations reach the target concentration C_s. However, the variance of the drug concentration depends critically on the magnitude of the ratio $2\alpha/\sigma^2$. If this ratio is less than or equal to 1, the variance at long times becomes indefinitely large, i.e., tends to infinity. The variance is finite when the ratio exceeds 1.

The existence of the critical monitoring frequency is a unique and somewhat unexpected prediction of the stochastic model that cannot be anticipated using deterministic models. However, in retrospect, this prediction is reasonable because an unmonitored processes will drift and if the intensity of the corrective actions is not sufficient to overcome the effects of

drift, then the variability in concentrations will be large. In Fig. 2, we plot the variance of the concentrations versus time with for varying values of σ. The initial value of drug concentration C_0 was set at 100, and the target concentration C_s was set at 150 and an α value of 1 per unit time was used. At small values of σ, the variance of concentrations reaches a plateau but when the σ value increases to point where $2\alpha/\sigma^2$ is less than 1, the variance increases indefinitely.

DISCUSSION

In this report, a stochastic model was used for quantitating the kinetics and variability with therapeutic drug monitoring. The model accounted for the variability inherent in the pharmacokinetics by allowing a geometric Brownian motion and the impact of the corrective actions was modeled by using "proportional control" term. The validity of the variability term was tested using experimental data from the seminal work on procainamide by Koch-Weser. The modeling framework is novel yet simple and structured enough to provide analytical results for the moments of the drug concentration probability density function.

A unique prediction of the stochastic model was that if the value of α does not exceed a critical value, the variance will increase indefinitely. From a dosing standpoint, such large variances are undesirable because some patients will be overdosed or underdosed. However, the value of α, the proportionality constant by which deviations from the target concentrations are converted to changes in infusion rate, is a factor that is directly under the caregiver's control. The model can potentially be used to select an α that keeps the variance at values that reduce the likelihood of toxic concentrations or underdosing. After α is selected, the drug concentration measured during therapeutic drug monitoring can readily be converted to changes in infusion rate.

As in all mathematical models, certain simplifying assumptions were necessary for the derivations. An important idealization is that corrective actions are taken continuously. Thus, the time scale predicted by Eq. (6) represents the lower limit that is achievable using a proportional control strategy with constant α values—in practice, because corrective actions in the therapeutic settings cannot be taken continuously, the time required to achieve the target concentration will generally be greater. Clearly, this continuous stochastic model represents a simplistic but useful first step toward building discrete stochastic models that reflect the clinical practice of therapeutic drug monitoring with greater realism. Discrete stochastic models involve stochastic difference equations and in addition to pharmacokinetic variability, they can be used to assess the impact of factors such as measurement error and time lag between measurement and corrective action.

In solving Eqs. (5) and (7), it was assumed that the initial concentrations were monodisperse. However, the mathematical framework is flexible and allows this assumption to be relaxed to accommodate distributions—the initial conditions for the ordinary differential Eqs. (5) and (7) are merely replaced by $E[C_0]$ and $E[C_0^2]$, respectively. For an initial concentration distribution that is log-normal with parameters (μ_0, σ_0), where μ_0 and σ_0 are the mean and the standard deviation of $\ln C_0$, respectively, the initial conditions are $E[C_0] = e^{(\mu_0+0.5\sigma_0^2)}$ and $E[C_0^2] = e^{2(\mu_0+\sigma_0^2)}$. Thus, stochastic models are flexible and general, and can provide information that is useful for the design of therapeutic regimens.

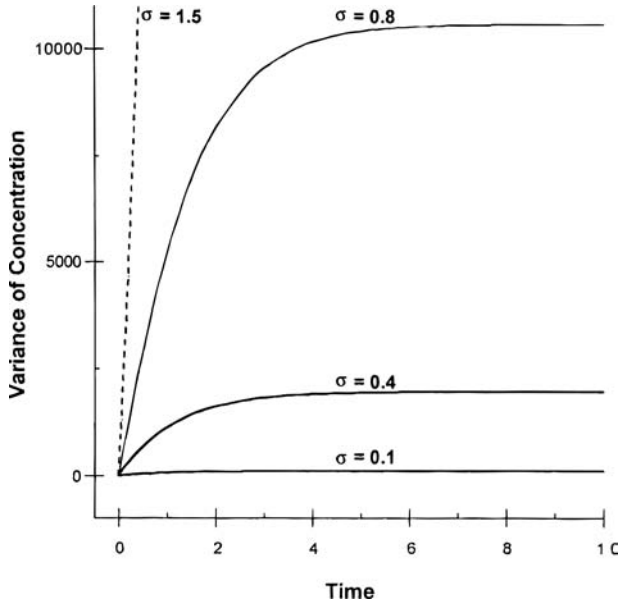

Fig. 2. The variance of the concentration as a function of time for the different values of σ indicated next to the curve for a monitored process. For the simulations, the value of α was equal to 1, in units of reciprocal time; the initial concentration, C_0, was 100 units, and the target concentration, C_s, was 150 units. The dashed line corresponds to $\sigma = 1.5$ which generates a $2\alpha/\sigma^2$ value that is less than 1 and causes the variance to increase indefinitely at large values of time.

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