A METHOD FOR ESTIMATING PHARMACOKINETIC RISKS OF
CONCENTRATION-DEPENDENT DRUG INTERACTIONS
FROM PRECLINICAL DATA

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ABSTRACT:
This article evaluates a novel approach for estimating the pharmacokinetic risks associated with drug interactions in populations. Preclinical pharmacokinetic and metabolism data are analyzed with a stochastic differential equation-based pharmacokinetic model that recognizes that the risks associated with known drug interactions involve deterministic and stochastic components. Specifically, a Bernoulli jump-diffusion pharmacokinetic model that accounts for the pharmacokinetics, the variability inherent in the pharmacokinetics, and the idiosyncratic nature of the possibility of drug interactions is proposed. In addition, the variability inherent in the extent of drug interaction is explicitly accounted for. The approach provides useful mechanistic insights into the stochastic processes that “drive” drug interactions in populations because it yields analytical results. The validity of the model predictions was tested with experimental data from two previously investigated systems: N-1 and N-3 caffeine demethylation in populations with smokers and in the terfenadine-ketoconazole system.

Assessing and managing the risks associated with drug interactions is important because most drug interactions are undesirable and represent significant costs for patients and their caregivers, drug companies, and society at large. Several prominent products have been withdrawn in recent years because of drug interactions, despite preclinical testing, and recent estimates of the prevalence of adverse drug reactions in hospitalized patients have attracted considerable media attention (Lesar et al., 1997; Lazarou et al., 1998).

The powerful numerical tools of parametric and nonparametric population pharmacokinetics are now routinely used to identify safe and effective dosing regimens and to individualize therapy (Rowland et al., 1985). For example, Grasela et al. (1987) used mixed-effect modeling prospectively on data from a clinical trial to detect an interaction between imipramine and alprazolam. The methods of population pharmacokinetics also are being increasingly used at the preclinical drug development stage. For example, Guzy and Hunt (1997) have suggested the use of computationally based population pharmacokinetic-pharmacodynamic models for preclinical use to determine the fraction of patients within a given therapeutic range.

Additionally, population pharmacokinetic methods, although extremely powerful and capable of extracting numerical values from noisy clinical trial data, tend not yield analytical results. Thus, a conceptual framework for a usable knowledge base can be built only after examination of a large number of simulations. In this article, a model for the population consequences of unanticipated drug interactions is developed. The modeling strategy is novel and takes into account the variability inherent in the concentrations of the drug, and the variability of the interaction-inducing agent effects as well as the idiosyncratic nature of drug interaction outcomes. Importantly, the model provides an analytical result that is potentially more useful and easier to use than numerical solutions, and provides mechanistic insight into the factors that increase the risk of interactions.

Derivations and Results
Assumptions. The risks associated with drug interactions have contributions from both deterministic and stochastic components. The deterministic component arises because drug pharmacokinetics cause drug concentrations to follow experimentally determinable trends even though the drug concentration at any given time is not completely determinate. The stochastic components can be further subdivided into two subtypes: the “continuous” stochastic process that characterizes the variability of the elimination rate constants of drugs, and idiosyncratic or unanticipated events characterized by discontinuous or “jump” processes caused by the interaction-inducing agent.

Herein, a one-compartment model is assumed. The interactions are assumed to cause abrupt increases in the elimination rate constant and the occurrence of the interaction events is assumed to have Poisson distribution. The occurrence of interactions is assumed to be independent of the continuous stochastic variability that is associated with drug concentrations.

The interaction event is assumed to abruptly change the elimination rate constant, resulting in proportional changes to the drug concentration profile. The interaction-induced decreases (or increases) in the elimination rate constant (represented by the symbol $Y$) are random variables that follow a log-normal distribution. Thus, in the model, both the fractional extent of the interaction effect and its occurrence are random variables. Additionally, it is assumed that the

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intake of interaction-inducing agent is accompanied with intake of sufficient drug so that the mass-balance requirements for the jump are fully met.

**Pharmacokinetic Model.** The stochastic Ito process (Ito, 1951) representing concentrations in a one-compartment pharmacokinetic model with unanticipated drug interactions can be expressed as follows:

$$\frac{dC}{C} = -Kdt + \sigma dz + (Y - 1)d\pi$$  \hspace{1cm} (1)

where \(K\) is the elimination rate constant or the trend rate constant in the absence of drug interactions; \(\sigma^2\) is the variance rate in the absence of the interaction-inducing agent; \(dt\) is differential time and \(dz\) is the differential of \(z\), the Wiener variable; and the Poisson jump variable, \(d\pi\), takes a value of 1 if the jump occurs (the probability of this is characterized by \(\lambda t\), where \(\lambda\) is the occurrence rate of interaction events, and \(t\) is time) and a value of zero if a jump does not occur. The \(-Kdt\) term characterizes the pharmacokinetic trend; the \(\sigma dz\) term characterizes the uncertainty caused by “usual garden-variety” variability or white noise, and \((Y - 1)d\pi\) represents the increased variability caused by the sudden, unanticipated arrival of the interaction. Upon the occurrence of an interaction, the elimination rate constant “jumps” instantaneously by \((Y - 1)\), causing the concentration to increase from \(C\) to \(CY\). Thus, the right-hand side of eq. 1 is a stochastically modified elimination rate constant that contains a Gaussian-distributed white-noise term \((\sigma dz)\) and a Poisson-distributed noise term \((Y - 1)d\pi\) caused by the interaction.

**Pharmacodynamic Model.** If the effect is a twice-differentiable function of only concentration and time, the stochastic process for the effect is also similar, and can be written as follows:

$$\frac{dE}{E} = -K_e dt + \sigma_E dz + (Y_k - 1)d\pi$$  \hspace{1cm} (2)

In eq. 2, the subscript \(E\) refers to effect. However, an extended version of Ito’s lemma can be used to derive the values for the drift rate and variance rate in terms of the pharmacokinetic parameters and pharmacodynamic effect equation.

$$K_e = -\frac{1}{E} \left( \frac{1}{2\sigma^2 C} \frac{\partial^2 E}{\partial C^2} - KC \frac{\partial E}{\partial C} + \frac{\partial E}{\partial t} \right)$$  \hspace{1cm} (3)

$$\sigma_E = \frac{1}{E} \left( \sigma C \frac{\partial E}{\partial C} \right)$$  \hspace{1cm} (4)

$$Y_k = \frac{E(CY)}{E(C)}$$  \hspace{1cm} (5)

The commonly used simple and sigmoid \(E_{\max}\) models are twice-differentiable functions of concentration alone, and the time partial derivative of effect with respect to time is zero, which allows the simplification of eq. 3 to:

$$K_e = -\frac{1}{E} \left( \frac{1}{2\sigma^2 C} \frac{\partial^2 E}{\partial C^2} - KC \frac{\partial E}{\partial C} \right)$$  \hspace{1cm} (6)

In the simple \(E_{\max}\) model, mean jumps in effect are likely to be more prominent with drugs that are used in the linear effect range, because \(Y_k\) will be larger. At saturation, the jumps in concentration will not result in jumps in effect.

**Effect of Interaction on Drug Concentration.** When the percentage change in drug concentration caused by the interaction-inducing agent is log-normally distributed, i.e., the jumps \(Y_j\) are random variables drawn from a log-normal distribution with mean \(\theta\) and variance \(\gamma^2\), the ratio \(C(t)/C_0\) also is log normally distributed. However, the variance parameter is Poisson distributed (Merton, 1976, 1990).

Additionally, because the mean \(\theta\) is the expectation \(\epsilon(\ln Y)\), not the arithmetic mean \(\epsilon(Y)\), the following relationship between the geometric mean and the arithmetic mean must be used to convert arithmetic mean quantities appropriately for use:

$$\ln \epsilon(Y) = \epsilon(\ln Y) + \frac{\gamma^2}{2} = \theta + \frac{\gamma^2}{2}$$  \hspace{1cm} (7)

Surprisingly, despite the discontinuous nature of the underlying stochastic processes, the distribution of concentrations is continuous. Press (1967) first provided analytical expressions for the probability density function of \(\ln C(t)\) but did not assume a deterministic trend. However, Beckers (1981) extended the Press equation to accommodate a deterministic trend. With these assumptions, the probability density function for concentration is stationary over time and is given by:

$$\frac{\ln C(t)}{C_0} \Rightarrow ^\infty \sum_{n=0}^\infty \frac{e^{-\ln(\lambda t)^n}}{n!} \mathcal{N}(-K_t + n\theta, \sigma^2\gamma + n\gamma^2)$$  \hspace{1cm} (8)

The symbol \(\Rightarrow\) should be read as “is distributed as” and the \(\mathcal{N}(-K_t n\theta, \sigma^2\gamma + n\gamma^2)\) is the probability density function of a normal distribution with mean \(-K_t n\theta\) and variance \(\sigma^2\gamma + n\gamma^2\).

The distribution in eq. 8 is a process that consists of Poisson events superimposed on events following another independent distribution that, in this case, happens to be log-normal. With the method of characteristic functions, the various moments of this distribution can be calculated (Press, 1967). The moments can be used to demonstrate that this distribution is leptokurtic. By definition, leptokurtosis implies that this distribution has a fatter tail than a comparable normal distribution, i.e., the probability of observing outlying high-concentration events is much greater than that for a normal distribution. Additionally, the skewness of the distribution is determined by \(\theta\), i.e., if \(\theta\) is negative, the distribution has negative skewness; if \(\theta\) is positive, the distribution has positive skewness; and if \(\theta\) is zero, the distribution is symmetric. The second moment or variance of the distribution in the presence of interactions is given by the following:

$$\text{Variance} = \left[ \sigma^2 + \lambda(\theta^2 + \gamma^2) \right] \lambda t$$  \hspace{1cm} (9)

The variance relationship (eq. 9) demonstrates that the variance in the presence of interactions is increased and that both the magnitude \(\lambda\) and the variability \(\sigma\) of the interactions are important.

More frequently, side effects from interaction-inducing agents are caused by drug concentrations exceeding the minimum toxic dose. To determine the probability \(P(\ln C > \ln C_t)\) of concentrations exceeding the minimum toxic dose, \(C_t\), the cumulative probability distribution function has to be calculated from eq. 8 as follows:

$$P(\ln C(t) > \ln C_t) = \int_{\ln C_t}^{\infty} \sum_{n=0}^\infty \frac{e^{-\ln(\lambda t)^n}}{n!} \mathcal{N}(-K_t + n\theta, \sigma^2\gamma + n\gamma^2)dx$$  \hspace{1cm} (10)
However, in eq. 9 only the terms containing the normal distribution are functions of concentration and

\[ P(\ln C(t) > \ln C_0) = \sum_{n=0}^{\infty} \frac{e^{-\lambda t}(\lambda t)^n}{n!} \left( 1 - \int_{-\infty}^{\ln C_0} N(-Kt + n\theta, \sigma^2 t + n\gamma^2) \, dx \right) \]

or alternatively,

\[ P(\ln C(t) > \ln C_0) = \sum_{n=0}^{\infty} \frac{e^{-\lambda t}(\lambda t)^n}{n!} \left( 1 - \Phi(-Kt + n\theta, \sigma^2 t + n\gamma^2) \right) \]

In eq. 11, \( \Phi(-Kt + n\theta, \sigma^2 t + n\gamma^2) \) is the cumulative probability distribution function of the normal distribution with mean \(-Kt + n\theta\) and variance \(\sigma^2 t + n\gamma^2\) evaluated at \(\ln C_0\).

In the limit of small values of \(\lambda t\), the Poisson process can be approximated by a Bernoulli process (Ball and Torous, 1983). The Bernoulli process is a model for interaction processes such that over a period of time, either no interaction occurs or just one interaction occurs. The cumulative probability density function for a Bernoulli mixture of Gaussians is as follows:

\[ P(\ln C(t) > \ln C_0) = (1 - \lambda t) \Phi(-Kt, \sigma^2 t) + \lambda t \Phi(-Kt + \theta, \sigma^2 t + \gamma^2) \]  

(12)

Thus, both models allow for discontinuous jumps but result in continuous distribution functions. In the following sections, eq. 12 is used because it is reasonable to assume that drug interactions are likely to be relatively rare events with small values of \(\lambda t\).

**Sensitivity of Interaction Probability to Parameters.** Sensitivity to time. The relationship between the time and the interaction probability is complex. The complexity is caused by two opposing factors: with increasing time, both the likelihood of an interaction and the likelihood of the emergence of individual variations increases, but this is offset by the decreases in drug concentration caused by the pharmacokinetic trend.

The predictions of eq. 12 for \(K\) values of 10, 1, 0.1, and 0.01 are summarized in Fig. 1. For these simulations, the interaction probability was set at 0.001 per unit time, and the variance rate \(\sigma^2\) of the elimination rate constant was set to 0.25 per unit time or 0.0625. The interaction probability was calculated assuming that concentrations 5-fold or greater than the initial concentration \(C_0\) were toxic. The \(\theta\) value or the mean value of the logarithm of the jump height was set to \(\ln 2\) and the variance of the jump heights, \(\gamma^2\), was set to 0.589, i.e., \(\gamma = 0.589\). B, relationship between \(K\) and interaction probability at time \(t = 1\). The solid line is an interpolated curve.

**Sensitivity to interaction frequency.** The cumulative probability of exceeding the toxic concentration is linearly related to jump frequency \(\lambda\), for small values of \(\lambda t\). This linear relationship can be derived in eq. 12 because the \(1 - \lambda t\) term can be Taylor series approximated by 1. The interaction probability as a function of \(\lambda\) is shown in Fig. 3A, and the simple linear relationship between \(I\) and the interaction probability is underscored in Fig. 3B.

**Sensitivity to jump height.** The dependence of the interaction probability on time with the jump height as a parameter is plotted in Fig. 4A. Figure 4B plots the interaction probability at time \(t = 1\) versus the jump height. The value of \(\gamma^2\), the variance of the interaction jump, was kept constant at 0.5(\(\ln 2\)) or 0.347. The values of \(\theta\), the mean of the
log-normal distribution of jump heights, were set to ln 1 or 0, ln 1.5, ln 2, or ln 5. These values were set to logarithmic values because they would correspond to arithmetic mean jump or $e(Y)$ values of 0, 50, 100, or 400% if the jumps were to be monodisperse, i.e., $\gamma = 0.589$. B, interaction probability as a function of $\sigma$ for time $t = 1$.

Sensitivity to jump height variability. The effect of jump height variability on the likelihood of interaction is summarized in Fig. 4. The mean logarithmic jump height, $\theta$, was kept constant at ln 2, and the variance of the logarithmic jump height, $\gamma^2$, was varied as a parameter between 0.1 and 0. The data in Fig. 4A show that even when the arithmetic mean value of the jump height is zero, there is still a risk of interaction. This “zero-jump height” risk occurs because the interaction-inducing agent increases the overall variance of the drug concentration. The interaction probability is a strong convex-increasing function of the jump height.

**Sensitivity to therapeutic index.** Drugs have a wide range of therapeutic indices, and the occurrence of concentration-dependent adverse events can reasonably be expected to be a function of the therapeutic index. To account for the therapeutic index, it was assumed that $C_0$ was in the therapeutic range and the effect of varying the ratio $C_t/C_0$ was examined in Fig. 6. The results in Fig. 6, A and B, show that interaction probability is a strong monotonically decreasing function of therapeutic index. A 6.67-fold increase in therapeutic index (1.5–10) causes the probability of interaction to diminish by approximately four orders of magnitude.

**Challenging Validity of Model.** Considerations in choice of test data set. Ideally, complete testing of the validity of this stochastic model requires histograms of pharmacokinetic profiles of drug in the presence of interaction-inducing agents that are administered randomly. The substantial published information on drug dose-independent hypersensitivity reactions was excluded because the model proposed focuses on drug concentration-dependent adverse events. Additionally, because this first-generation model does not yet directly account for polymorphism in drug-metabolizing enzymes, data in-

FIG. 2. Interaction probability defined in eq. 12 as a function of time for the different values of $\sigma^2$ and interaction probability as a function of $\sigma$ for time $t = 1$.

A, interaction probability defined in eq. 12 as a function of time for the different values of $\sigma$. The values of $\sigma$ used are shown against the corresponding lines. For these simulations, the elimination rate constant was set at 1 per unit time, and the interaction probability was set at 0.001 per unit time. The interaction probability was calculated assuming that concentrations 5-fold or greater than the initial concentration $C_0$ were toxic. The $\theta$ value or the mean value of the logarithm of the jump height was set to ln 2, and the variance of the jump heights, $\gamma^2$, was set to 0.56, i.e., $\gamma = 0.589$. B, interaction probability as a function of $\sigma$ for time $t = 1$.

FIG. 3. Interaction probability defined in eq. 12 as a function of time for the different values of $\lambda$ and interaction probability as a function of $\lambda$ for time $t = 1$.

A, interaction probability defined in eq. 12 as a function of time for the different values of $\lambda$. The values of $\lambda$ used are shown against the corresponding lines. For these simulations, the elimination rate constant was set at 1 per unit time, and the variance rate $\sigma^2$ of the elimination rate constant was set to 0.25 per unit time. The interaction probability was calculated assuming that concentrations 5-fold or greater than the initial concentration $C_0$ were toxic. The $\theta$ value or the mean value of the logarithm of the jump height was set to ln 2, and the variance of the jump heights, $\gamma^2$, was set to 0.56, i.e., $\gamma = 0.589$. B, interaction probability as a function of $\lambda$ for time $t = 1$. The solid line is a linear fit to the data.
volving substantially polymorphic metabolism, e.g., dextromethorphan metabolism by cytochrome (CYP)\(^1\) 2D6, also were excluded.

The approach adopted to test the model was to use studies of drug metabolism in populations involving smokers, and the data reported by Carrillo and Benitez (1994) were used. This approach was selected because smoking is known to cause changes in the concentrations of drug, and in nonhospitalized patient populations, it can be viewed as a potential source of “interaction” that occurs randomly after drug intake.

Brief description of data set. Carrillo and Benitez (1994) studied the metabolism of caffeine in 107 healthy Spaniards and reported the distribution of the metabolite ratios for N-1, N-3, and N-7 demethylation. Each demethylation metabolite ratio index used was constituted with multiple metabolites; the details are described in Carrillo and Benitez (1994). An advantage of the data set was that histogram data for both smokers and nonsmokers were presented, and specific hypotheses regarding both groups and the entire sample could be examined. The N-3 demethylation pathway mediated by CYP1A2 accounts for 80% of caffeine metabolism. CYP1A2 is not considered to be polymorphic. Carrillo and Benitez (1994) reported that N-1 and N-3 methylation were affected by smoking but that N-7 was not significantly different.

Testable hypotheses. To challenge the model in the context of the information provided by Carrillo and Benitez (1994), answers to four questions were sought: 1) are the interacting and noninteracting populations described as a sum of log-normal distributions, 2) is the variance of drug concentrations in the presence of smoking-induced interactions greater than in the absence of interactions, 3) is the sign of the skewness the same as the sign of \(\theta\) (the model predicts that the skewness of the overall distribution has the same sign as the sign of the skewness of the interacting population), and 4) is the distribution of drug concentrations in the presence of smoking-induced interactions leptokurtic as predicted by the model?

Results. The data provided in the article by Carrillo and Benitez (1994) were analyzed. The N-1, N-3, and N-7 demethylation metabolite index histograms for smokers and nonsmokers were analyzed.
and N-3 interactions are greater in smokers than in nonsmokers in Tables 1 and 2. The N-7 metabolite ratios that were not modified by smoking did not show increased standard deviations in smokers. Thus, the numerical trends of the standard deviations in smokers are consistent with the model.

Is the skewness of the overall distributions determined by the sign of the \( \theta \), the mean of the log-normal jump distribution? For N-1 demethylation (Table 1), the skewness of the distribution in smokers is positive, the nonsmoker distribution is slightly negative, and the overall distribution has positive skewness. For N-3 demethylation (Table 2), the skewness of the distribution in smokers is positive, and the nonsmoker distribution is more negative but the overall distribution is positive. These numerical trends are consistent with the model predictions for skewness. Finally, as shown in Table 1 and 2, the overall distribution is leptokurtic, i.e., has positive values for the kurtosis, for both N-1 and N-3 demethylation. Thus, all the moments for N-1 and N-3 demethylation of caffeine show trends that are consistent with the model.

The variance for N-3 demethylation of caffeine increases from 0.28 to 0.36 upon smoking (Table 2), but the increase in the variance for N-1 demethylation of caffeine is relatively smaller: from 0.3 to 0.32 (Table 1). However, the numerical trends for all the higher order statistical moments are all also consistent with the model for both N-1 and N-3 metabolism, and taken together, the results provide support for the assumptions and structure of the model.

Using the Model. The interaction between terfenadine and ketoconazole is widely known to cause significant changes in the serum concentration of terfenadine through a mechanism involving CYP3A4 inhibition (Yun et al., 1993; von Moltke et al., 1994). The resulting increased serum terfenadine concentrations cause a prolongation of the cardiac ventricular contraction interval and can result in death from torsades des points, a rare, life-threatening ventricular arrhythmia (Honig et al., 1993; Peck et al., 1993).

To adduce evidence for the reasonableness of the proposed model, the distribution of terfenadine concentrations in the presence and absence of ketoconazole was determined with data from the literature. In the absence of drug interaction-inducing agents, it is known that terfenadine concentrations in blood are undetectable except by sensitive mass spectrometric assays (Coutant et al., 1991; Woosley et al., 1993). It was reasoned that the plausibility of the model would be supported if the probability of toxic terfenadine concentrations was negligibly small in the absence of ketoconazole and increased dramatically in its presence.

Modeling parameters. The simulations were carried out with the data in Honig et al. (1993). Because ketoconazole is taken once daily and is prescribed in 0.2% of the terfenadine prescriptions, the \( \lambda \) value was set to 0.002/(24 h/day − 8 h sleep) = 1.25 \times 10^{-4} \text{ h}^{-1}.

The values of \( \theta \) and \( \gamma \) were determined from von Moltke et al. (1994), who studied the interaction between these two drugs in microsomal preparations. The therapeutic range of ketoconazole is 1 to 5 \( \mu \)g/ml or 1.88 to 9.40 \( \mu \)M, and von Moltke et al. (1994) calculated that the average area under the curve or, equivalently, the average terfenadine concentrations would increase by a factor of 12.8 \pm 2.3 (\( n = 6 \); mean \pm S.E.) and 59.4 \pm 11.5 (\( n = 6 \); mean \pm S.E.) at 1 and 5 \( \mu \)g/ml ketoconazole, respectively. The \( \gamma \) value used was 0.2771.

The \( \gamma \) was calculated by carrying out 200 Monte Carlo simulations to generate 200 sets, each containing six normally distributed random variables with a mean of 59.4 and a standard deviation of 11.5 \( \gamma \). The average standard deviation of the natural logarithms of the 200 sets of six random variables yielded \( \gamma \). The numerical value of \( \gamma \) used was 0.4046 and was calculated from the arithmetic mean, 59.4, and the value of \( \gamma \) from eq. 7. The value of \( C_0 \) was set to 1.3 ng/ml, which is

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A \quad \lambda = 0.001 \\
\theta = 0.693 \\
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B \quad \lambda = 0.001 \\
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F I G . 6 . \text{ A, interaction probability defined in eq. 12 as a function of time for the different values of the therapeutic index and interaction probability as a function of } C_{\text{ nasal}/C_0 \text{ for time } t = 1.}
\]

with the Kolmogorov-Smirnov test to test the null hypothesis that the underlying distributions were log-normal. The results for N-1 and N-3 demethylation metabolite indices are summarized in Fig. 7. The results for N-7 demethylation are not shown because Carrillo and Benitez (1994) did not report significant differences between smokers and nonsmokers for this pathway. The \( x \)-axis in Fig. 7 is the observed cumulative probability and the \( y \)-axis is the cumulative probability that would be expected if the natural logarithm of the demethylation metabolite ratio were normally distributed. The linearity of the distributions for smokers and nonsmokers suggests, albeit subjectively, that log-normal distributions are a good approximation. The \( P \) values for a Kolmogorov-Smirnov test also are indicated in Fig. 7. The \( P \) values were not significant, showing that the model-predicted log-normal distribution is a statistically acceptable approximation.

Because log-normal distributions can arise in a variety of circumstances, additional signatures that would assist in validating the model were sought. The various moments for the distributions of the logarithm of the ratios of N-1, N-3, and N-7 demethylation metabolites are shown in Tables 1, 2, and 3, respectively.

Is the variance of drug concentrations in the presence of smoking-induced interactions greater than in the absence of interactions? The numerical values of the sample standard deviations for significant N-1

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\text{Fig. 6. A, interaction probability defined in eq. 12 as a function of time for the different values of the therapeutic index and interaction probability as a function of } C_{\text{ nasal}/C_0 \text{ for time } t = 1.}
\]
the $C_{\text{max}}$ for terfenadine in humans and the toxic concentration was assumed to be 20 ng/ml (Honig et al., 1993; von Moltke et al., 1994).

The value of $\sigma$ was estimated by fitting the pooled data from the study by Honig et al. (1993) with the modeling program Adapt II (D’Argenio and Schlumitzky, 1992). A one-compartment linear model with first order absorption and elimination parameters defined as rate constants was used. The variance model used included a constant term to account for the interindividual variability caused by differences in initial concentration and a $\sigma C t$ term to represent the white-noise variability. Based on the modeling, the value of $\sigma$ was calculated to be 0.1039 h⁻¹.

Figure 8 summarizes the predictions of the jump-diffusion model for the terfenadine-ketoconazole interaction. Figure 8A is a plot of the probability of encountering a toxic dose of terfenadine in the presence and absence of ketoconazole as a function of time. The control is negligibly small compared with the probability predicted in the presence of ketoconazole.

Figure 8B plots the terfenadine concentration on the $x$-axis and the cumulative probability, $P(C>x)$, on the $y$-axis. The distributions are calculated at 4 h in the presence and absence of ketoconazole. The solid square with the error bar represents the mean ± 2 S.D. concentrations that were reported by Okerholm et al. (1981) in 14 healthy volunteers and can be considered the therapeutic range of concentrations observed in the absence of interactions. The model predicts that the probability of achieving a therapeutic terfenadine concentration in the control is high but that the probability of exceeding a concentra-
The open circle with error bars encompassing a shaded region represents the mean terfenadine concentration greater than that on the x-axis at in the presence of ketoconazole. B, probability of observing a 4-h terfenadine concentrations in the presence of interaction-inducing agent. The model accounted for the variability inherent in the pharmacokinetic and pharmacodynamic interactions: the proposed model complements these methods by providing a framework for estimating the likelihood of these interactions.

Clearly, the model integrates both pharmacokinetic and population factors in a coherent and easy-to-understand mechanistic model of interactions. The proposed method has the advantage of providing insights into the interaction risks with data that are routinely obtained during the drug development process. For example, the elimination rate constant ($k$) and its variance rate ($\sigma^2$) can be obtained from clinical trials in the absence of interaction-inducing agent. As a first approximation, the distributional properties of the jump process can be scaled up from the percentage inhibition values obtained in experiments with purified or recombinant CYP-450 microsomes. This was demonstrated by using $\theta$ values derived from the results of von Moltke et al. (1994) who estimated the average concentrations from microsome data. An important additional advantage of the proposed approach is that it is “distribution-generating” in the sense that the probability distribution of the drug concentrations is generated by the mechanism and does not have to be externally imposed.

A Monte Carlo simulation was used for extracting the values of $\theta$ and $\gamma$ from the report by von Moltke et al. (1994). In practice however, the Monte Carlo simulation can be eliminated because the raw data are usually available and the two parameters, $\theta$ and $\gamma$, can be calculated directly by a log transformation and subsequent calculations of the mean and standard deviations of log-transformed data. For the analysis reported herein, only the descriptive statistics, the arithmetic mean and standard deviation, were available, necessitating the simulation.

The model provides a simple, intuitive picture of drug interactions. However, its simplicity is both a strength and a weakness; it is a strength because it yields analytical results and a weakness because some of the assumptions offer the potential for further improvement.
In the following, specific assumptions and their impact on the drug concentration probability distribution functions are discussed. The assumption that the increases in drug concentration occur instantaneously enough to be characterized as “jump” process is a mathematical idealization. Clearly, because drug interactions are likely to take a finite time to impact drug concentrations, the probability of interactions is likely to be underestimated on account of this assumption. The assumption may, however, not have significant impact when the interaction-inducing agent acts on hepatic drug metabolism, is extensively extracted on its first pass through the liver, and exerts its effects on the drug-metabolizing enzymes immediately. The model assumes that the drug of interest is administered once and the occurrence of the interaction is “hit-or-miss.” Efforts are currently underway to extend the findings to the scenario in which the drug is dosed to steady state and the interaction occurs sporadically. The Press (1967) model may capture many features of this dosing situation, but further refinements may be necessary.

Drugs that are substrates of polymorphic enzymes such as CYP2D6 and CYP2C19 (Eichelbaum and Gross, 1990; Benet et al., 1996) have an additional, independent source of variability arising on account of the polymorphism, and their concentration probability distributions, even in the absence of any interaction-inducing agent, are distinctly bimodal (or multimodal). Because the model eq. 1 has only one Gaussian distributed (drdz) term, more sophisticated models are needed for substrates of polymorphic enzyme systems. Surprisingly, because of the Lindberg-Levy Central Limit theorem (Lindeberg, 1922; Levy, 1925), the limiting case of a drug whose clearance is determined by a large number of possibly polymorphic enzymes may be amenable to the treatment proposed in this article because the presence of polymorphisms in this context can be accounted for by increasing the variance rate.

There is considerable interest in the role of presystemic intestinal CYP-450s and P-glycoprotein on drug disposition and pharmacodynamics. For example, the triazolobenzodiazepines triazolam (T1/2 = 3 h) and alprazolam (T1/2 = 15 h) exhibit differential susceptibility to inhibition by ketoconazole (Greenblatt et al., 1998). The inhibition of presystemic P-450s causes larger increases on the Cmax of triazolam than the Cmax of alprazolam and the clinical impact of the ketoconazole interaction is more intense on triazolam pharmacodynamics. At first sight, because triazolam has the shorter half-life, these data might imply the triazolabenzodiazepines triazolam (1/2 = 3 h) and alprazolam (1/2 = 15 h) exhibit differential susceptibility to inhibition by ketoconazole (Greenblatt et al., 1998). The inhibition of presystemic P-450s causes larger increases on the Cmax of triazolam than the Cmax of alprazolam and the clinical impact of the ketoconazole interaction is more intense on triazolam pharmacodynamics. At first sight, because triazolam has the shorter half-life, these data might appear to be a contradiction of the model proposed in this article. They are not. The results in this report focus on the ratio C/C0 and do not directly account for the variability in C0, the systemic concentration. However, it is likely that the analytical results of the model can be easily extended to the case where C0 also is also log normally distributed and is currently being investigated. The “jump-diffusion” model can be extended to more complex situations, but the added complexity may necessitate numerical solution.

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References