An Application of Ito's Lemma in Population Pharmacokinetics and Pharmacodynamics

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INTRODUCTION

Numerical methods of analysis have contributed significantly to our current understanding of population pharmacodynamics and pharmacokinetics. These approaches are powerful and are capable of extracting parameter estimates from data (1). However, one disadvantage of using purely numerical methods is that there are relatively few intuitive analytical results to guide reasoning about population pharmacodynamics—a usable knowledge base can be built only after extensive examination of a large number of simulations.

In this report, a result from the theory of stochastic calculus with potential application to population pharmacokinetics and pharmacodynamics is highlighted. Specifically, Ito's lemma (2) (a lemma is mathematical terminology for a subsidiary theorem) is used to derive an equation for the effect of population pharmacokinetic variability in a one-compartment pharmacokinetic model coupled to a non-linear E_{max} model of pharmacodynamics.

Theoretical derivations are used to demonstrate that for a first-order process, a log-normal distribution of concentrations results from normally distributed elimination rate constants. Useful formulae for calculating the drift rate and variance rate for the effect in the non-linear E_{max} model for effect are also derived.

DERIVATIONS AND RESULTS

Ito's Lemma

Ito's lemma is central to stochastic problems that are functions of generalized Wiener processes (2). An Ito process is a stochastic process that can be expressed as:

$$dx = a(x, t)\,dt + b(x, t)dz$$

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. For a function f(x,t), Ito's lemma is the stochastic calculus equivalent of the chain rule in deterministic calculus and states that:

$$df = \left(a\frac{\partial f}{\partial x} + \frac{\partial f}{\partial t} + \frac{b^2}{2}\frac{\partial^2 f}{\partial x^2}\right)dt + \frac{\partial f}{\partial x}bdz$$

Thus, the function f also follows an Ito process with a drift rate of:

$$\left(a\frac{\partial f}{\partial x} + \frac{\partial f}{\partial t} + \frac{b^2}{2}\frac{\partial^2 f}{\partial x^2}\right)$$

and a variance rate of $b^2(\partial f/\partial x)^2$. Also, notice that the same stochastic variable z, contributes to both x and its function f.

First-Order Pharmacokinetics and Ito's Lemma

In pharmacokinetics, the x of interest is the drug concentration, C. For a first-order pharmacokinetic process with elimination rate constant K:

$$a(x, t) = -KC$$

If the square root of the variance rate function, b(x,t), of the system is characterized by a constant coefficient of variation, σ, then:

$$b(x, t) = \sigma C$$

According to these assumptions, the variance of drug concentration is σ^2C^2t, and the standard deviation at a given time is proportional to concentration. This model for variance rate accounts for the observation that the absolute variations in concentration tend to be larger at larger concentration values and that the variability in a given patient is also a function of time. The term σ^2 represents the variance rate of the concentrations changes when these changes are expressed as a percentage of the absolute concentration. Alternatively, σ^2 represents the variance rate of the elimination rate constant. With these assumptions, the stochastic total differential expression for drug concentration is:

$$dC = -KC\,dt + \sigma C\,dz$$

The population pharmacokinetic implications of these assumptions for dC are now examined using the derivation in Hull (3). Consider the function $f = \ln C$, using Ito's lemma.

Because $(\partial \ln C)/\partial C = 1/C$, $(\partial \ln C)/\partial t = 0$, and $(\partial^2 \ln C)/\partial C^2 = -1/C^2$, the process followed by d(ln C)is:

$$d(\ln C) = -\left(K + \frac{\sigma^2}{2}\right)dt + \sigma dz$$

Since K and σ are constants, the equation shows that the change in ln C between the current time t, and any future time T, is normally distributed with a mean drift rate of $-(K + \sigma^2/2)$ and a variance rate of σ^2. Equivalently, concentrations are log-normally distributed in a first order process in which the square root of the variance rate function has a constant coefficient of variation.

Saturable E_{max} Pharmacodynamics and Ito's Lemma

The objective of this section is to derive an analytic expression for the contribution of pharmacokinetic variability to pharmacodynamic variability in a direct effect E_{max} pharmacodynamic compartment that responds to the first-order process.

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Let the pharmacodynamic effect, E, be described by the Michaelis-Menten type E_{max} model:

$$E = \frac{E_{max}C}{EC_{50} + C}$$

Because

$$\frac{\partial E}{\partial C} = \frac{E_{max}EC_{50}}{(EC_{50} + C)^2} = \frac{E^2}{C^2}\frac{EC_{50}}{E_{max}}, \frac{\partial \ln C}{\partial t} = 0,$$

and

$$\frac{\partial^2 E}{\partial C^2} = -\frac{2E_{max}EC_{50}}{(EC_{50} + C)^3} = -2\frac{E^3}{C^3}\frac{EC_{50}}{E_{max}^2},$$

the process followed by the pharmacodynamic effect compartment in the absence of intrinsic pharmacodynamic variability is:

$$dE = \left(-K\frac{E^2}{E_{max}}\frac{EC_{50}}{C} - \sigma^2\frac{E^3}{E_{max}^2}\frac{EC_{50}}{C}\right)dt + \sigma\frac{E^2EC_{50}}{E_{max}C}dz$$

The variance rate of the pharmacodynamic process is thus:

$$\sigma^2\left(\frac{EC_{50}}{C}\right)^2 E_{max}^2\left(\frac{E}{E_{max}}\right)^4 \text{ or equivalently, } \left(\frac{\sigma E_{max}(C/EC_{50})}{(1 + (C/EC_{50}))^2}\right)^2$$

In the linear range, i.e., for values of $C << EC_{50}$, the pharmacodynamic variance rate caused by pharmacokinetic variability is:

$$\left(\frac{\sigma E_{max}C}{EC_{50}}\right)^2$$

Thus, it follows that in systems with linear effect, the effect square root of variance rate function is also proportional to concentration. At concentrations near effect compartment saturation, i.e., $C >> EC_{50}$, the pharmacodynamic variance rate is given by:

$$\left(\frac{\sigma EC_{50}E_{max}}{C}\right)^2$$

Figure 1 plots the function $(C/EC_{50})/(1 + (C/EC_{50}))^2$ against normalized concentration C/EC_{50}. The variability reaches a maximum when the derivative $(1/(EC_{50} + C)^2 - 2C/(EC_{50} + C)^3 = 0)$ or $C = EC_{50}$. The maximum value of $(C/EC_{50})/(1 + (C/EC_{50}))^2$ is 0.25; therefore the square root of the variance rate function for the pharmacodynamics reaches a maximal value of $0.25\sigma E_{max}$.

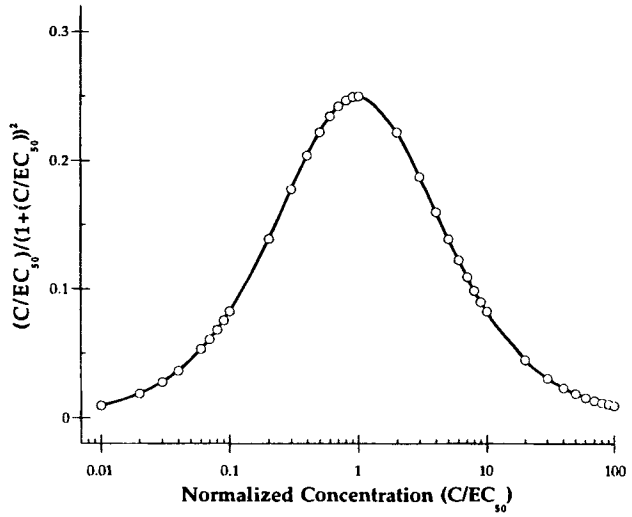

Fig. 1. Figure 1 plots the function $(C/EC_{50})/(1 + (C/EC_{50}))^2$ which contributes to the observed variability of pharmacodynamics in the E_{max} model.

Example: Linear Effect Kinetics in First-Order Systems with Logarithmic Concentration-Effect Curves

It is well known that for many drugs, a linear decay with time of pharmacodynamic effects is possible even when the time course of drug concentration decay is exponential (4). The occurrence of linear effect kinetics in systems with logarithmic dose-response curves was highlighted by Levy in (5).

Now consider a drug that follows the previously used stochastic pharmacokinetic equation:

$$dC = -KC\,dt + \sigma C\,dz$$

Levy showed that effect followed linear time decay if the relationship between effect and concentration was described by an equation of the form:

$$E = m \ln C + d$$

In the above equation, m and d are the slope and intercept, respectively, of the effect versus ln C line. Now let us apply Ito's lemma to this well known effect relationship:

$$dE = -m\left(K + \frac{\sigma^2}{2}\right)dt + m\sigma dz$$

This stochastic equation represents the logarithmic effects in a system with first-order drug elimination. By putting σ to zero, it becomes evident that this equation is consistent with Levy's finding for deterministic systems. Thus, the Ito's lemma approach yields the well known linear effect kinetics result as a special case. However, the equation also extends the Levy's linear effect kinetics finding to systems with stochastic pharmacokinetic variability because it shows that in the absence of intrinsic pharmacodynamic variability, the effect is normally distributed when the concentration distribution is log-normal.

DISCUSSION

In this report, I demonstrate two useful applications of Ito's lemma in population pharmacokinetics and pharmacodynamics and derive mathematically rigorous analytical expressions that can be used to obtain intuitive insights into drug development and public policy problems. Ito's lemma has not been previously examined in the context of drug effects but is frequently used in financial economics and is central to the derivation of the famous Black-Scholes model of option pricing (6).

These results provide additional mechanistic insight into the origins of the log-normal distribution in pharmacokinetics. The log-normal distribution appears frequently in population pharmacokinetics and even the Food and Drug Administration statistical test for bioequivalence assumes log-normal distributions. However, this prevalence of the log-normal distribution in pharmacokinetic data is somewhat intriguing given that the Lindeberg-Lévy Central Limit Theorem (which is central to all parametric statistics) predicts that the distribution of sums and

sample means from all populations approaches a normal distribution in the limit of large sample size (7,8). According to the Ito's lemma derivation shown here, drug concentrations are log-normally distributed in first-order processes whose square root of variance rate function is characterized by a constant coefficient of variation.

Levy first demonstrated that the sensitivity of E_{max} pharmacodynamic models to drug concentration variations was greatest around the EC_{50} value (9). In pharmacodynamic models with the sigmoid E_{max} or Hill-type response curves, sensitivity is also highest around the EC_{50} value and systems with higher values for the Hill coefficients exhibit greater sensitivity to variations in concentrations (9,10). Arguments based on the slope of the response curves were used for the estimation. Hoffman and Goldberg (11) have also examined the effect of receptor micro-heterogeneity on the shape of Hill type response curves. The findings in this report are qualitatively consistent with those previously reported by these authors but clearly, the Ito's lemma method accounts not only for the sensitivity of the effect model but also for the variance structure of the pharmacokinetic inputs. It might be argued that Ito's lemma has merely confirmed what was already known using slope arguments: however, it should be pointed out that Ito's lemma method provided the tools for determining *both* the instantaneous slope and the trend. Thus, the method is also very general and is easily extended.

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