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Application of Queueing Theory to Pharmacokinetics

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Abstract □ This paper considers the steady-state plasma drug concentration in a one-compartment, open pharmacokinetic model with multiple doses and first-order kinetics using a classical deterministic technique as well as a queueing theoretical stochastic analysis. The stochastic analysis employs a new method for obtaining the steady-state probability distribution of the content of a dam with compound Poisson input and a general release rule. It is shown that if the deterministic steady-state average concentration exists, it is equal to the mean value of the steady-state concentration, the probability distribution of which is obtained using the stochastic model. Moreover, the steady-state probability distribution of the concentration and its mean always exist in the stochastic model. Ramifications of the stochastic method of analysis are discussed.

Keyphrases □ Pharmacokinetics—steady-state plasma drug concentration, queueing theory □ Models, pharmacokinetic—steady-state plasma drug concentration, queueing theory □ Queueing theory—application to pharmacokinetics, steady-state plasma drug concentration

This paper introduces a method of analyzing drug accumulation based on a stochastic model of multiple-dosing regimens. In classical pharmacokinetic theory, transient and steady-state drug concentrations in the blood for multiple-dosing regimens are derived from knowledge of the deterministic dose sizes, intervals between doses, volumes of distribution, and kinetics of elimination and transfer between body compartments (1–4). This analysis may be clinically useful only if two major conditions are true: (*a*) the dosage intervals are known, and (*b*) the amount of drug absorbed as a consequence of each dose is known.

These conditions rarely are met in practice. As noted previously (2), nonstandard definitions of *bid*, *tid*, and *qid* may lead to varying dosage intervals. Family physicians and drug package inserts often direct that drugs should be taken near meal times, bed time, or three or four times daily without defining these terms specifically (2). Patients rarely take drugs on schedule unless they are in the hospital. Furthermore, dose size may vary because the initial dose or other doses may be different from the usual maintenance dose. The fractional absorption of oral drugs depends on several factors. For drugs administered intramuscularly, the fractional absorption partially depends on the injection site (1). Moreover, completeness of drug absorption always is clinically important (1, 5).

These observations suggest the desirability of obtaining the drug concentration in the plasma when the dose intervals, doses, or absorption fractions are subject to random fluctuations and must be considered random variables. Accounting for such random variations in these parameters leads to the consideration of a stochastic analysis of pharmacokinetic models. This paper emphasizes the new technique itself rather than its application to general multiple-dosing models. The model presented is a one-compartment, open model with instantaneous input and first-order elimination. A classical, well-known deterministic method of analysis is presented for convenience of reference, and a stochastic, queueing theoretical approach for studying the same model then is given. The latter technique is based on a new method of analyzing the model of a dam with a general release rule[1], which was studied previously in stochastic processes using other approaches.

THEORETICAL

The Model—The model treated is a one-compartment, open model with multiple dosing and first-order kinetics (1–4, 6). For clarity and to focus attention on the new technique, very rapid administration of each dose directly into and instantaneous distribution throughout the compartment is assumed. This assumption is a good approximation for intravenous bolus dosing. For outpatient oral dosing (to which the stochastic technique is more applicable), first-order absorption may be a more appropriate assumption. However, for many drugs in common clinical use, the absorption constant is appreciably larger than the elimination constant. Examples are digoxin, sublingually administered nitrites, salicylates, and phenylbutazone. For such drugs, the assumption of instantaneous absorption, although only approximate, is not entirely unreasonable.

The following notations are used in both the deterministic and stochastic analyses:

V = volume of compartment
K_e = elimination rate constant (time^{-1})
$t_{1/2e}$ = elimination half-life; $1/k_e = t_{1/2e}/\ln 2 = 1.44t_{1/2e}$
τ_n = administration time of nth dose, $n = 1, 2, 3, \ldots$; $\tau_1 = 0$
T_n = nth dosage interval; $T_n = \tau_{n+1} - \tau_n$
D_n = amount of nth dose
F_n = fraction of D_n distributed throughout V
E_n = effective increase in drug concentration at time τ_n; $E_n = F_nD_n/V$
$C(t)$ = drug concentration at time t; $t \geq 0$
C_n = drug concentration at time τ_n; $C_1 = C(0) = 0$
λ = rate of administration of doses
B = common distribution function of effective increases in concentration, E_n, independent of n; $B(0) = 0$
$r(x)$ = drug elimination rate when the concentration is x (mass times volume^{-1} times time^{-1})

Deterministic Analysis—The following well-known deterministic analysis is presented for comparison with the stochastic analysis. Vari-

[1] P. H. Brill, unpublished data.

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ations and generalizations of this analysis were given previously (1–4, 6). Equations 1–9 in the present discussion parallel formulas presented previously. All of the parameters are considered deterministic so that T_n, D_n, F_n, E_n, and C_n are real nonnegative constants for $n = 1, 2, 3, \ldots$. The deterministic differential equations of elimination are:

$$\frac{dC(t)}{dt} = -K_e C(t) \qquad \tau_n < t \leq \tau_{n+1} \qquad \text{(Eq. 1)}$$

with initial conditions $C(\tau_n^+) = C_n + E_n$, $n = 1, 2, 3, \ldots$ (3). It then follows that:

$$C(t) = (C_n + E_n) \exp[-K_e(t - \tau_n)] \qquad \tau_n < t \leq \tau_{n+1},\ n = 1, 2, 3, \ldots \qquad \text{(Eq. 2)}$$

and thus:

$$C_{n+1} = C(\tau_{n+1}) = (C_n + E_n) \exp(-K_e T_n) \qquad n = 1, 2, 3, \ldots \qquad \text{(Eq. 3)}$$

Three sequences are of interest in pharmacokinetics: minimum (or infimum), maximum (or supremum), and average concentrations during each dosage interval, which are C_n, $C_n + E_n$, and $\overline{C}_n = (1/T_n) \int_{t=\tau_n}^{\tau_{n+1}} C(t)\, dt$, respectively. Consideration of general constraints on the parameters E_n and T_n that are necessary and sufficient for the convergence of these sequences to limiting values is outside the scope of this paper. However, a sufficient (but not necessary) condition for any of these sequences to converge is monotonicity (*i.e.*, always increasing or always decreasing) after some finite value of n. For different dosing regimens, the limits of all three, any two, only one, or none of these sequences may exist. In the remainder of this section, all limits are taken as $n \to \infty$.

If $\lim C_n$ exists, Eq. 3 yields:

$$\lim C_n = \lim\{E_n/[\exp(K_e T_n) - 1]\} \qquad \text{(Eq. 4)}$$

If $\lim (C_n + E_n)$ exists, Eq. 3 yields:

$$\lim (C_n + E_n) = \lim\{E_{n+1}/[1 - \exp(-K_e T_n)]\} \qquad \text{(Eq. 5)}$$

Using Eq. 2 and substituting from Eq. 3 result in:

$$\overline{C}_n = (1/T_n) \int_{t=\tau_n}^{\tau_{n+1}} C(t)\, dt = (1/K_e)(C_n + E_n - C_{n+1})/T_n \qquad \text{(Eq. 6a)}$$

and, hence, if $\lim \overline{C}_n$ exists:

$$\lim \overline{C}_n = (1/K_e) \lim [(C_n + E_n - C_{n+1})/T_n] \qquad \text{(Eq. 6b)}$$

With the assumption that $\lim \overline{C}_n$ and $\lim C_n$ exist, it follows from Eq. 6*b* that:

$$\lim \overline{C}_n = (1/K_e) \lim (E_n/T_n) = (1/K_e) \lim (F_n D_n/T_n) \qquad \text{(Eq. 7)}$$

If both $\lim \overline{C}_n$ and $\lim (C_n + E_n)$ exist, then:

$$\lim \overline{C}_n = (1/K_e) \lim (E_{n+1}/T_n) = (1/K_e) \lim (F_{n+1} D_{n+1}/T_n) \qquad \text{(Eq. 8)}$$

In Eqs. 4–8, E_n and T_n must be known to predict whether the sequences will converge or oscillate. Knowledge of these parameters rarely is obtainable, except possibly in controlled hospital situations or laboratory studies. In pharmacokinetic literature, analytical results for these limits usually are derived by assuming uniform dosing, *i.e.*, $F_n = F$, $D_n = D$, and $T_n = T$, so that the E_n values all are equal. The condition of uniform dosing is sufficient but not necessary for the limits in Eqs. 4–8 to exist. Under uniform dosing, the steady-state average concentration is given by:

$$\lim \overline{C}_n = 1.44 t_{1/2e} E/T = 1.44 t_{1/2e} FD/(VT) \qquad \text{(Eq. 9)}$$

Since actual dosing rarely is uniform in ambulatory patients, even when it is the intended therapy, nonuniform dosing must be considered. A generalization of Eq. 9 holds for nonuniform dosing of the following type. Both $\lim C_n$ and $\lim \overline{C}_n$ are assumed to exist, so Eq. 7 holds. In addition, let the average increase in drug concentration per dose after n intervals, which is given by $(\sum_{i=1}^n E_i)/n$ (or equivalently by $\sum_{i=1}^n F_i D_i/n$), and the average dose interval after n intervals, $(\sum_{i=1}^n T_i)/n$, tend to the limits E' $[\equiv (FD)']$ and T', respectively, as $n \to \infty$. Then, with Eq. 7 and the fact that both E_n and T_n are bounded away from zero and also bounded above, the following is obtained:

$$\lim \overline{C}_n = (1/K_e) \lim (E_n/T_n) \qquad \text{(Eq. 10a)}$$

$$\lim \overline{C}_n = (1/K_e) E'/T' \qquad \text{(Eq. 10b)}$$

$$\lim \overline{C}_n = 1.44 t_{1/2e} E'/T' \qquad \text{(Eq. 10c)}$$

$$\lim \overline{C}_n = 1.44 t_{1/2e} (FD)'/T' \qquad \text{(Eq. 10d)}$$

The introduction of this type of nonuniform dosing model serves a dual purpose. First, it leads to Eqs. 10*c* and 10*d*, which demonstrate that the limiting average concentration depends on the effective increases in concentration and the dose intervals only through their respective limiting average values. Second, it links the deterministic models of this section to the stochastic model. The latter model also possesses the property established in Eqs. 10*c* and 10*d*.

Stochastic Analysis—In this section, a completely different method for analyzing the present model is introduced. The parameters T_n, D_n, and F_n, $n = 1, 2, \ldots$, are considered to be sequences of independently, identically distributed, random variables, so that $E_n = F_n D_n/V$ is a random variable. Hence, $\{C_n, n \geq 1\}$ and $\{C(t), t \geq 0\}$ are stochastic processes.

Furthermore, it is assumed that $\{N(t), t \geq 0\}$ is a Poisson process with arrival rate λ, where $N(t)$ denotes the number of doses in the time interval $[0, t]$. Note that $P[N(t) = k] = [e^{-\lambda t}(\lambda t)^k]/k!$, $k = 0, 1, 2, \ldots$. Thus, $\{T_n, n \geq 1\}$ is a sequence of exponentially distributed random variables with the common probability distribution function $1 - \exp(-\lambda x)$, $x \geq 0$. The sequence $\{E_n, n \geq 1\}$ is assumed to have common probability distribution, B, with $B(0) = 0$. The mean value of the random variable with distribution B is denoted by $E'' = \int_{z=0}^{\infty} z\, dB(z)$. The drug elimination is described by a general release function, r, with $r(c) > 0$ for $c > 0$ and $r(0) = 0$, where c denotes the concentration level. Therefore, the pharmacokinetic system previously modeled deterministically is modeled stochastically as a dam with a general release rule[1] (7–9). Hence, in general, the following analysis is not constrained to first-order kinetics of elimination. Sample functions of the process $\{C(t), t \geq 0\}$ satisfy the differential equations:

$$dC(t)/dt = -r[C(t)] \qquad \tau_n < t \leq \tau_{n+1} \qquad \text{(Eq. 11)}$$

with initial conditions $C(\tau_n^+) = C_n + E_n$, $n = 1, 2, 3, \ldots$.

The relation $\lim_{c \to \infty} r(c) > \lambda \int_0^\infty z B(dz) = \lambda E''$ guarantees the existence of the steady-state probability distribution function of the drug concentration (8). This result implies, as will be seen following Eq. 15, that for first-order kinetics the steady-state concentration, its probability distribution, and its average always exist. This probability distribution function is denoted by G having the probability density function g. An equation for G that is well known in the literature of stochastic processes (7–9) now is derived by a new method[1]. The present investigators believe that this method has strong intuitive appeal as well as other desirable properties that are outside the scope of this paper. This method differs from one given previously (9), which counts crossings of levels during regenerative cycles of the process rather than during time intervals of the form $(0, t]$, as is done here. Let $E[D_t(c)]$ and $E[U_t(c)]$ denote the expected values of the number of times that a sample function of the process $\{C(t), t \geq 0\}$ downcrosses and upcrosses level c, respectively, during time interval $(0, t]$. The theorems given previously[1] state that:

$$\lim_{t \to \infty} E[D_t(c)]/t = r(c) g(c) \qquad c > 0 \qquad \text{(Eq. 12)}$$

and:

$$\lim_{t \to \infty} E[U_t(c)]/t = \lambda \int_{z=0}^{c} \overline{B}(c - z) G(dz) \qquad \text{(Eq. 13)}$$

where $\overline{B}(x) = 1 - B(x)$, $x \geq 0$. Since the number of downcrossings and upcrossings cannot differ by more than one during any time interval, it follows that the right sides of Eqs. 12 and 13 must be equal, so that[1] Eq. 14 holds:

$$r(c) g(c) = \lambda \int_{z=0}^{c} \overline{B}(c - z) G(dz) \qquad \text{(Eq. 14)}$$

This relation is the well-known equation in stochastic processes referred to previously (7–9). Up to this point, the release function, r, has not been specified so that Eq. 14 holds for non-first-order kinetics of elimination. At this stage, Eq. 14 is specialized to first-order kinetics of elimination by assuming that:

$$r(c) = K_e c \qquad c \geq 0 \qquad \text{(Eq. 15)}$$

Notice that $\lim_{c \to \infty} K_e c = \infty$, which is greater than $\lambda E''$ since E'' is finite. Therefore, with first-order elimination, the limiting probability distribution and its average always exist (8). This property of the stochastic model obviates the need to consider the convergence properties of the sequences in Eqs. 4–8. The actual observed increases in concentration per dose and actual observed dosage intervals encountered in any particular therapy will vary in accordance with sampling from distribution B and from an exponential distribution, respectively. Due to the law

of large numbers, their averages will tend to E'' and $1/\lambda$, respectively, as the number of doses increases. Therefore, this model is the stochastic analog of a deterministic model with the type of nonuniform dosing considered preceding Eq. 10*a*. Thus, the stochastic model does not assume that the intended therapy must involve uniform dosing, but it also applies if the intended therapy actually happens to comprise uniform dosing. This result follows since uniform dosing is just a special type of deterministic nonuniform dosing considered following Eq. 9. To apply the stochastic model for drug management in a given therapy, it must be established that there is a known probability distribution, B, and that the number of doses in any time interval has a Poisson distribution.

With Eq. 15, Eq. 14 reduces to:

$$K_e c g(c) = \lambda \int_{z=0}^{c} \overline{B}\,(c - z) g(z)\, dz \qquad \text{(Eq. 16)}$$

whose tractability without using integral transforms depends on the nature of the function B. Even if Eq. 16 is not readily solvable for g, the steady-state mean value of the concentration with probability density g can be found immediately by integrating both sides of Eq. 16 with respect to the variable c over the range $(0, \infty)$. This integration leads to:

$$\overline{C} = \lambda E''/K_e = 1.44 t_{1/2e} E'' \lambda \qquad \text{(Eq. 17)}$$

where $\overline{C}$ is the mean value of the steady-state probability distribution of the drug concentration. If D_n and F_n are completely independent sequences of random variables, then $E'' = F''D''/V$, where F'' and D'' are the mean fractional absorption and mean dosage, respectively. In this case, setting $\lambda = 1/T''$ transforms Eq. 17 into:

$$\overline{C} = 1.44 t_{1/2e} F''D''/(VT'') \qquad \text{(Eq. 18)}$$

Comparison of Eqs. 9, 10*c*, and 10*d* with Eqs. 17 and 18 demonstrates that $\lim \overline{C}_n = \overline{C}$, provided $\lim \overline{C}_n$ exists. A complete solution of Eq. 16 is given when the effective increases in concentration at dose times are exponentially distributed with the mean $1/\mu$, *i.e.*, $B(x) = 1 - \exp(-\mu x), x \geq 0$. Substitution of this B into Eq. 16 yields:

$$K_e c g(c) = \lambda \int_{z=0}^{c} \exp[-\mu(c - z)] g(z)\, dz \qquad \text{(Eq. 19)}$$

Operating on Eq. 19 with differential operator $\langle D + \mu \rangle$, solving the resulting differential equation, and using the normalizing condition $\int_{z=0}^{\infty} G(dz) = 1$ (or proceeding as in Example 1 of Ref. 7) result in the following solution:

$$g(c) = \exp(-\mu c)(\mu c)^{(\lambda/K_e - 1)}\, \mu/\Gamma(\lambda/K_e) \qquad c > 0 \quad \text{(Eq. 20)}$$

where Γ denotes the gamma function. This result was obtained previously by several investigators (8, 10). In this example, Eq. 17 becomes $\overline{C} = 1.44 t_{1/2e} \lambda/\mu = 1.44 t_{1/2e} F''D''/(VT'')$ as in Eq. 18. This relation expresses the fact that $\overline{C}$ is exactly the same as the classical steady-state average concentration in Eq. 9 or its generalization in Eq. 10*d*, if the latter limits exist.

DISCUSSION

The steady-state probability distribution function of drug concentration and its average always exist and have been calculated under the assumptions that dose administrations occur in a Poisson process, fractional absorptions and dose amounts are independent random variables, the common probability distribution of the resulting drug concentration increases at dose times is known, and elimination is first order. The probabilistic approach presented might be used to predict the percentage of the time that a patient's drug concentration will be below or above any level in the steady state. Imprecise knowledge of the deterministic sequences of doses, dosage intervals, and the resulting limiting behavior of the concentration in the compartment is quantified by exact knowledge of the steady-state probability distribution function.

Using classical theory, one simply predicts a patient's minimum, maximum, or average drug concentration; in addition, it is assumed that the dosage intervals and absorption characteristics are precisely known constants. In classical theory, one can predict, for example, that if a patient takes 500 mg of procainamide every 4 hr, his or her serum level will "likely" be therapeutic because these constants are rarely known exactly. It would be more informative and useful to know that if the patient takes the drug *approximately* every 4 hr and if drug absorption is subject to chance variations, then the serum will contain an established therapeutic concentration 95% of the time.

The latter type of prediction might allow more rational therapy with drugs taken by ambulatory patients for which the therapeutic effect is close to toxicity or for which it is essential to maintain a therapeutic serum level. Digoxin, antiarrhythmics, anticonvulsants, certain antibiotics, antineoplastics, aminophylline, salicylates in the therapy of rheumatic disorders, antihypertensives, and corticosteroids are examples of medications belonging to this class. The particular stochastic analysis presented here may be directly applicable to some of these agents, particularly those with relatively rapid absorption and first-order elimination kinetics.

Similarly, the stochastic approach can be used to predict caffeine levels in coffee and tea drinkers since these beverages usually are imbibed at random intervals and by sipping random amounts. Carbon monoxide and nicotine levels in tobacco users and ethanol levels in partygoers might be predicted in the same manner. The exponential dam described by Eq. 19 might be a good model for these situations, and Eq. 20 then would be an exact analytical solution for the steady-state probability distribution of the serum concentration. The dosage rate, λ, and the average increase in concentration, $1/\mu$, would have to be determined experimentally.

Extension of the present analysis to include first-order absorption would make the probabilistic technique applicable to a broader class of drugs. Moreover, development of similar queueing theoretical methods for multicompartment models with more general dosing regimens is of interest.

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