Rapid Compartment- and Model-Independent Estimation of Times Required to Attain Various Fractions of Steady-State Plasma Level during Multiple Dosing of Drugs Obeying Superposition Principle and Having Various Absorption or Infusion Kinetics

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Abstract □ A new general equation based only on plasma data was derived for rapid estimation of the average plasma level and the mean fraction of the steady-state plasma level attained during any multiple-dosing interval. It can be applied to any complex absorption or infusion kinetics (*i.e.*, is not limited to zero-order or first-order kinetics) for drugs obeying linear disposition kinetic or superposition principles. The time, t, required to reach a certain mean fraction of the steady-state plasma level is equal to the time at which the plasma area from time zero to time t is equal to the same fraction of the plasma area from time zero to infinity ($AUC_{0\to\infty}$) following a single dose. No other pharmacokinetic parameters are necessary.

Keyphrases □ Plasma drug levels—rapid estimation of times required to attain various fractions of steady-state level, pharmacokinetics □ Drug absorption—estimation of times required to attain various fractions of steady-state level, pharmacokinetics □ Models, pharmacokinetic—times required to attain various fractions of steady-state plasma drug level

Accumulation profiles (times required to reach various mean fractions of the steady-state plasma level after multiple dosing) are important in drug therapy and animal and human toxicity studies. Most reported equations for predicting the accumulation profiles based on linear pharmacokinetics appear to be limited to classical one-compartment or two-compartment models with multiple (parallel) first-order absorption or with multiple intravenous bolus injection or short-time infusion (1–7). They usually require information such as the apparent volumes of distribution, the first-order intercompartmental distribution rate constants, the first-order elimination rate constant from the central compartment, the absorption rate constant, and the terminal first-order elimination rate constant. Equations will certainly become more complicated if more than a two-compartment open model is involved or if the absorption process cannot be described simply by zero-order or first-order equations.

The purpose of this article is to describe a novel compartment- and model-independent method for rapidly estimating the average plasma level and the times to obtain various mean fractions of the steady-state plasma level during multiple dosing. This method is based on the superposition principle (2, 3, 5, 8). It can be applied to any absorption or infusion kinetics, no matter how complex.

THEORETICAL

Following a single dose, the total area under the plasma level–time curve during each successive interval separated hypothetically by one dosing interval, T, is represented by $AUC_{0\to T}$, $AUC_{T\to 2T}$, $AUC_{2T\to 3T}$, . . . , $AUC_{(n-1)T\to nT}$. The cumulative area from time zero to time nT after a single dose is represented by $AUC_{0\to nT}$. The plasma area data after a single dose can be estimated by either the integration method or the linear or logarithmic trapezoidal rule methods (9, 10). The total areas under the plasma level–time curve during the first, second, third, . . . , nth dosing intervals after multiple dosing are denoted by AUC_{1T}, AUC_{2T}, AUC_{3T}, . . . , AUC_{nT}, respectively.

Based on the superposition principle, the total area during each interval after multiple dosing can be calculated by (2, 3, 5, 8):

$$AUC_{1T} = AUC_{0\to T} \quad \text{(Eq. 1)}$$

$$AUC_{2T} = AUC_{0\to T} + AUC_{T\to 2T} = AUC_{0\to 2T} \quad \text{(Eq. 2)}$$

$$AUC_{3T} = AUC_{0\to T} + AUC_{T\to 2T} + AUC_{2T\to 3T} = AUC_{0\to 3T} \quad \text{(Eq. 3)}$$

$$AUC_{nT} = AUC_{0\to T} + AUC_{T\to 2T} + \ldots + AUC_{(n-1)T\to nT} = AUC_{0\to nT} \quad \text{(Eq. 4)}$$

When n is large or approaching infinity, $AUC_{0\to nT}$ approaches $AUC_{0\to\infty}$, the total AUC from time zero to infinity obtained after a single (maintenance) dose. Therefore, the average steady-state plasma level, $\overline{C}_{pss}$, can be calculated by (2, 3, 5, 8):

$$\overline{C}_{pss} = \frac{AUC_{0\to\infty}}{T} \quad \text{(Eq. 5)}$$

and the average plasma level during the nth dosing interval of the multiple dosing should be equal to:

Table I—Hypothetical Plasma Level Data after a Single Oral Dose to a Subject

t, hr	Plasma Level, mg/liter	$AUC_{t1\to t2}$, hr mg/liter	$AUC_{0\to t}$, hr mg/liter	f^a
0	0	—	—	
0.5	0	0	0	0
1.0	2	0.5	0.5	0.0006
2.0	6	4.0	4.5	0.0054
3.0	10	8.0	12.5	0.0150
5.0	10	20.0	32.5	0.0390
10.0	9	47.5	80.0	0.0961
24.0	9	126.0	206.0	0.2475
48.0	8	204.0	410.0	0.4926
72.0	7	180.0	590.0	0.7088
96.0	3.5	121.2	711.2[b]	0.8544
120.0	1.75	60.6	771.8[b]	0.9272
144.0	0.875	30.3	802.1[b]	0.9636
∞		30.3	832.4[c]	1.0000

[a] $f = AUC_{0\to t}/AUC_{\infty}$. [b] Area estimated by the logarithmic trapezoidal rule method (11). [c] Area estimated by the extrapolation method using a half-life of 24 hr.

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$$\bar{C}_{pnT} = \frac{AUC_{0\to nT}}{T} \quad \text{(Eq. 6)}$$

Therefore, the mean fraction of the steady-state plasma level, f, achieved during the nth dosing interval should be equal to:

$$f = \frac{AUC_{0\to nT}}{AUC_{0\to\infty}} \quad \text{(Eq. 7)}$$

DISCUSSION

Equation 7 indicates that if a time of nT is needed to obtain an f fraction of $AUC_{0\to\infty}$ after a single dose, it also would take that long to obtain the same mean fraction of $\bar{C}_{pss}$ during the nth interval after multiple dosing. Equation 7 also indicates that the time to reach a certain mean fraction of $\bar{C}_{pss}$ is independent of the dosing interval. The terminal biological half-life of a drug *per se* does not affect the time required to reach a certain f value.

The major advantages of this new approach are simplicity, generality, and the elimination of many pharmacokinetic parameters commonly calculated after oral and intravenous administrations. The only information needed is the compartment- and model-independent plasma area data obtained after a single-dose study.

A hypothetical example illustrates the application of this new method. The hypothetical plasma level data after administration of a single oral dose to a subject and the data analyses based on Eq. 7 are summarized in Table I. The plasma level profile is very difficult, if not impossible, to describe by an equation. When the same dose is given every 12 hr, the average plasma levels between 60 and 72 hr and between 108 and 120 hr will be 70.88 and 92.72% of the steady-state plasma level, respectively (Table I). The steady-state plasma level should be equal to 69.37 mg/liter (*i.e.*, 832.4/12). On the other hand, the average plasma levels between 48 and 72 hr and between 96 and 120 hr will still be 70.88 and 92.72% of the steady-state plasma level, respectively, if the dose is given every 24 hr. The steady-state plasma level, however, will be reduced to only 50% of 69.37 mg/liter. This new method can also be applied when there is a lag time in absorption, as shown in the example.

For drugs obeying nonlinear pharmacokinetics, such as phenytoin, a new factor, the apparent volume of distribution, can also affect the times required to reach various fractions of the steady-state plasma level after multiple dosing (11).

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Determination of Ethylene Oxide, Ethylene Chlorohydrin, and Ethylene Glycol Residues in Ophthalmic Solutions at Proposed Concentration Limits

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Abstract □ A GLC method was developed for the determination of ethylene oxide and its two reaction products, ethylene chlorohydrin and ethylene glycol, in ophthalmic solutions at the levels recently proposed by the Food and Drug Administration. The method requires no extractions, sample preparations, or elaborate trapping and concentrating techniques. All three components can be chromatographed on the same spiral glass column packed with a porous polymer adsorbent.

Keyphrases □ Ethylene oxide—analysis, GLC, ophthalmic solutions □ Ethylene chlorohydrin—analysis, GLC, ophthalmic solutions □ Ethylene glycol—analysis, GLC, ophthalmic solutions □ GLC—analysis, ethylene oxide, ethylene chlorohydrin, ethylene glycol, ophthalmic solutions

The Food and Drug Administration (FDA) recently published (1) proposed rules governing maximum residue limits for ethylene oxide (I) and its two reaction products, ethylene chlorohydrin (II) and ethylene glycol (III), in drugs and medical devices. These rules apply to ophthalmic solutions, for which maximum residue levels of 10, 20, and 60 ppm have been established for I, II, and III, respectively. These levels, proposed in conformance with current good manufacturing practices for finished pharmaceuticals, have been necessitated by the known toxicity and/or the mutagen potential of these compounds. Thus, while I is a highly effective sterilant, significant residues of it can be harmful. Its two reaction products, II, produced from ethylene oxide and free chloride ion, and III, an ethylene oxide hydrolysis product, also are harmful in significant amounts.

Ophthalmic solutions that are not treated with I but that contact treated package cap liners must be assayed for residue content according to the proposed specifications. This paper describes a successful attempt to satisfy this objective.

BACKGROUND

Extensive GLC work has been done on ethylene oxide (I) singly and in combination with its reaction products in various items including foods, fabrics, pharmaceuticals, medical and surgical devices, and plastics

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