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Noncompartmental Analysis Based on Statistical Moment Theory

Throughout this text we have used noncompartmental methods for the estimation of certain pharmacokinetic parameters without specifically referring to them as such. These methods are usually based on the estimation of the area under a plot of drug concentration versus time. Noncompartmental methods have been used to estimate bioavailability, clearance, apparent volume of distribution, and the fraction of a dose of a drug that is converted to a specific metabolite, based on data following single doses of drug and metabolite. These methods have also been used to predict the average steady-state concentration of a drug or its metabolites, based on data following a single dose of the drug, and the time required to reach a given fraction of the steady-state concentration when a fixed dose of a drug is given at regular intervals.

Noncompartmental methods do not require the assumption of a specific compartmental model for either drug or metabolite. In fact, these methods can be applied to virtually any compartmental model, provided that we can assume linear pharmacokinetics. Noncompartmental methods are hardly new. However, the idea that noncompartmental methods provide a general approach for pharmacokinetic analysis is both new and important. During the preparation of this edition of *Pharmacokinetics*, there has been a distinct shift away from computer-based curve-fitting of experimental data and elaboration of compartmental models and toward noncompartmental methods of analysis. In the final stages of preparation of the text, this shift was so evident, that the authors concluded that a separate section dealing with the subject matter was required. Therefore, this chpater has been added in proof. The scope of this chapter is by necessity limited: we shall briefly introduce the basis for noncompartmental analysis, summarize the various noncompartmental methods that have been presented in different sections of the text, modestly extend the applications of noncompartmental analysis, and, perhaps, provide some direction for future developments.

STATISTICAL MOMENTS

Statistical moments have been used extensively for data analysis in chemical engineering [1]. One of the earliest applications to biological systems was provided by Perl and Samuel [2] in a report concerned with the kinetics of body cholesterol. In 1975 Oppenheimer et al. [3] applied statistical moments to the analysis of iodothyronine metabolism and distribution in man. The application of statistical moments to pharmacokinetics was reported in 1979 by Yamaoka et al. [4] and Cutler [5]. In 1980, Riegelman and Collier [6] applied statistical moment theory to the evaluation of drug absorption.

The time course of drug concentration in plasma can usually be regarded as a statistical distribution curve [1]. Irrespective of the route of administration, the first three (zero to second) moments are defined as follows:

$$\text{AUC} = \int_0^\infty C\,dt \tag{11.1}$$

$$\text{MRT} = \frac{\int_0^\infty tC\,dt}{\int_0^\infty C\,dt} = \frac{\text{AUMC}}{\text{AUC}} \tag{11.2}$$

$$\text{VRT} = \frac{\int_0^\infty t^2 C\,dt}{\int_0^\infty C\,dt} = \frac{\int_0^\infty (t - \text{MRT})^2\,C\,dt}{\text{AUC}} \tag{11.3}$$

where MRT is the mean residence time and VRT is the variance of the mean residence time of a drug in the body. AUC, MRT, and VRT are termed the zero, first, and second moment, respectively, of the drug concentration-time curve. The area under the curve of a plot of the product of concentration and time versus time from zero time to infinity is often referred to as the area under the (first) moment curve, AUMC [7]. The moments defined above can be calculated by numerical integration using the trapezoidal rule (see App. D) from concentration-time data following drug administration. Only the zero and first moments have been used in pharmacokinetic analysis because the higher moments are prone to an unacceptable level of computational error.

In the usual single-dose pharmacokinetic study, blood sampling is stopped at some time t^* when drug concentration, C^*, is measurable. Hence, estimation of the area under the blood level-time curve from zero time to infinity, AUC, must be carried out in two steps. The area under the curve from zero time to t^* is calculated by means of the trapezoidal rule. To this partial area we must add the area under the curve from t^* to infinity, which is usually estimated as follows:

$$\int_{t^*}^{\infty} C\,dt = \frac{C^*}{\lambda_n} \tag{11.4}$$

where λ_n is 2.303 times the slope of the terminal exponential phase of a plot of log drug concentration versus time. The sum of the two partial areas is AUC.

The same approach must be used to estimate total AUMC. The area under the first moment curve from t* to infinity is estimated as follows [7]:

$$\int_{t^*}^{\infty} tC\,dt = \frac{t^*C^*}{\lambda_n} + \frac{C^*}{\lambda_n^2} \tag{11.5}$$

BIOAVAILABILITY

Bioavailability often refers to the fraction (F) of an oral dose that actually reaches the systemic circulation. Since the availability of an intravenous dose is usually unity, we can estimate F as follows:

$$F = \frac{D_{i.v.}AUC_{oral}}{D_{oral}AUC_{i.v.}} \tag{11.6}$$

Hence, F is simply the ratio of the zero moments after oral and intravenous (i.v.) administration, respectively, adjusted for differences in the size of the dose. Equation (11.6) assumes equal clearances in the oral and intravenous studies. The fraction of the oral dose available relative to a standard other than an intravenous injection (F_r) may be estimated by means of a similar equation.

CLEARANCE

Increasingly, clearance is viewed as the single most important parameter to describe the pharmacokinetics of a drug. One can define clearance as the reciprocal of the zero moment of a blood level-time curve normalized for dose. In other words,

$$Cl = \frac{D_{i.v.}}{AUC} \tag{11.7}$$

Clearance is usually calculated after an intravenous dose ($D_{i.v.}$) of a drug, but may sometimes be calculated after intramuscular administration. Clearance cannot be estimated after oral administration of a drug unless it can be assured that the total dose reaches the systemic circulation.

For drugs that are completely absorbed from the gastrointestinal tract and that are eliminated only by metabolism in the liver, the ratio of oral dose to AUC is equal to the hepatic intrinsic clearance of the drug. Under certain conditions intrinsic clearance may be related to the V_{max} and K_m of the drug-metabolizing enzyme process.

HALF-LIFE

The first moment of the blood level-time curve, mean residence time, is the statistical moment analogy to half-life ($t_{1/2}$). In effect, the MRT represents the time for 63.2% of the administered dose to be eliminated. Therefore, the MRT of a drug that can be described by a one-compartment model after intravenous administration is given by the following equation [3]:

$$MRT_{i.v.} = \frac{1}{K} \tag{11.8}$$

where K is the first-order elimination rate constant. It follows that

$$t_{1/2} = 0.693 \cdot MRT_{i.v.} \tag{11.9}$$

The MRT of a drug that distributes slowly and requires multicompartment characterization is a function of the model rate constants for distribution and elimination. However, in noncompartmental terms the following relationship is useful [7].

$$MRT_{i.v.} = \frac{1}{\overline{K}} \tag{11.10}$$

where $\overline{K}$ is a first-order rate constant equal to the ratio of clearance to apparent volume of distribution at steady state (V_{ss}). For drugs requiring multicompartment characterization, $\lambda_1 < \overline{K} < \lambda_n$. It may be appropriate in most instances to consider the product of 0.693 and $MRT_{i.v.}$ as the *effective* half-life of a drug requiring a multicompartment model.

Irrespective of the distribution characteristics of drug, MRT represents the time for 63.2% of a intravenous bolus dose to be eliminated. As such, it may be possible to estimate MRT from urinary excretion data alone by determining the time required to excrete 63.2% of that amount of the dose which is ultimately excreted in the urine.

Mean residence time is a function of how a drug is administered. MRT values for noninstantaneous administrations will always be greater than the MRT following intravenous bolus administration. However, $MRT_{i.v.}$ may sometimes be estimated following other modes of drug administration. For example, following a short-term constant-rate intravenous infusion, the first moment of the blood level-time curve is given by

$$MRT_{inf} = MRT_{i.v.} + \frac{T}{2} \tag{11.11}$$

where T is the infusion time. Therefore, MRT_{inf} can be calculated from the data according to Eq. (11.2), and $MRT_{i.v.}$ may be estimated by rearranging Eq. (11.11).

ABSORPTION KINETICS

Statistical moment methods for estimating rates of absorption after oral or intramuscular administration of a drug are based on differences in mean residence times after different modes of administration [5]. In general,

$$MAT = MRT_{ni} - MRT_{i.v.} \tag{11.12}$$

where MAT is the mean absorption time, MRT_{ni} is the mean residence time after administration of the drug in a noninstantaneous manner, and $MRT_{i.v.}$ is the mean residence time after intravenous bolus administration.

When drug absorption can be described by a single first-order process,

$$MAT = \frac{1}{k_a} \tag{11.13}$$

where k_a is the apparent first-order absorption rate constant. Under these conditions the absorption half-life is given by

$$\text{Absorption } t_{1/2} = 0.693 \cdot MAT \tag{11.14}$$

When drug absorption is a zero-order process,

$$MAT = \frac{T}{2} \tag{11.15}$$

where T is the time over which absorption takes place.

Deconvolution, described in Chap. 4, is another example of the application of statistical moment theory for the estimation of absorption kinetics. Riegelman and Collier [6] have applied statistical moment theory to the gastrointestinal absorption of a drug after oral administration of a solid dosage form. Their analysis permits the estimation of a mean dissolution time of a drug from its dosage form.

APPARENT VOLUME OF DISTRIBUTION

Of the many parameters used to describe drug distribution, the most useful is the apparent volume of distribution at steady state, V_{ss}.

According to statistical moment theory [3,7], V_{ss} is simply the product of clearance and mean residence time, after a single intravenous bolus dose of a drug. Therefore,

$$V_{ss} = Cl \cdot MRT = \frac{D_{i.v.} \cdot AUMC}{AUC^2} \tag{11.16}$$

Although Eq. (11.16) applies only to intravenous bolus administration, the relationship can be modified easily to accommodata other modes of drug administration [8]. If a drug is given by a short-term constant rate intravenous infusion [9], then

$$V_{ss} = \frac{\text{infused dose} \cdot AUMC}{AUC^2} - \frac{\text{infused dose} \cdot T}{2 \cdot AUC} \tag{11.17}$$

where T is the infusion time. Since the infused dose is equal to the product of the zero-order infusion rate, k_0, and T, we can also express Eq. (11.17) as follows:

$$V_{ss} = \frac{k_0 T \cdot AUMC}{AUC^2} - \frac{k_0 T^2}{2 \cdot AUC} \tag{11.18}$$

FRACTION METABOLIZED

It is sometimes useful to know the fraction of a dose of a drug that is converted to a certain metabolite. An unambiguous estimation requires that a single dose of both drug and metabolite be admimistered [10]. Although statistical moment theory does not reduce the experimental difficulties in making this estimation, it does facilitate the analysis.

It can be shown that the fraction metabolized, F_m, to a specific metabolite is simply equal to the ratio of the zero moment of the metabolite level-time curve after administering the drug to the zero moment of the metabolite level-time curve after administering an equimolar dose of the metabolite [10]:

$$F_m = \frac{AUC'_x}{AUC'} \tag{11.19}$$

where AUC'_x is the area under the curve of metabolite concentration in plasma versus time from zero time to infinity after an intravenous dose of the drug, and AUC' is the total area under the metabolite concentration-time curve after an equimolar intravenous dose of the metabolite.

PREDICTING STATE-STATE CONCENTRATIONS

When a dose of a drug is repetitively given at regular intervals, the area under the drug concentration-time curve during a dosing interval at steady state is equal to the total area under the curve after a single dose. Therefore, we can demonstrate that the average drug concentration at steady state, which is equal to the area under the drug level-time curve during a single dosing interval at steady state divided by the duration of the dosing interval, can be estimated after a single dose of the drug according to the following equation:

$$\bar{C} = \frac{AUC}{\tau} \tag{11.20}$$

where AUC is the total area under the curve after a single dose and τ is the dosing interval.

The ratio of metabolite to drug concentration at steady state can also be predicted after a single dose of the drug [11,12]. This requires determination of the zero moment of both the metabolite level- and drug level-time curves after administering the drug (see Chap. 8).

PREDICTING TIME TO STEADY STATE

To carry out a pharmacokinetic analysis at steady state, or to determine whether a patient is stabilized after continuous administration of a drug, we must be able to estimate the time required for the drug concentrations in plasma to reach some substantial fraction (e.g., 90–99%) of the steady-state concentration. For drugs that distribute rapidly and can be described by a one-compartment model, the time to reach a certain fraction of steady state is a relatively simple function of the half-life of a drug. The situation is more complicated for drugs that require multicompartment characterization. Statistical moment theory provides a unique solution to this problem. Chiou [13] has recently shown that by means of area analysis one can predict the time to reach a given fraction of steady state from a single dose administered in the same way that will be used for repetitive dosing. In essence, the time required, after giving a single dose, for the partial area under the curve, AUC_0^t, to be equal to a certain fraction of the total area under the curve, AUC, is the same as the time required to reach the same fraction of steady-state on repetitive dosing of the drug [14]. This relationship is expressed in the following equation:

$$f_{ss} = \frac{AUC_0^t}{AUC} \tag{11.21}$$

where f_{ss} is the fraction of the steady-state reached at time t on repetitive dosing, and the area terms refer to a single dose.

CONCLUSIONS

This overview of noncompartmental methods based on statistical moment theory, albeit circumscribed, is sufficient in our view to demonstrate the power of the approach. It is evident that statistical moment theory permits a wide range of analyses that, in most instances, will be adequate to characterize the pharmacokinetics of a drug.

There are, of course, certain problems that are not addressed by this theory. Nonlinear events are not adequately treated at this time by statistical moment theory. Statistical moments provide only limited information regarding the time course of drug concentrations; for the most part, we deal with averages. However, we point out that other types of noncompartmental methods such as superposition (see App. E) can be used to augment statistical moment theory in this case.

We strongly suspect that future developments will remove many of the limitations that now exist. We predict that these trends in pharmacokinetic analysis, coupled with the impressive developments in microcomputer technology, will remove the reliance on main frame computers and may make compartmental analysis a matter of historical interest.

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