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# Statistical Moments in Pharmacokinetics: Models and Assumptions

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**Abstract**—The modelling basis of statistical moments in pharmacokinetics is considered and the associated assumptions and restrictions highlighted. Both deterministic and statistical models are described and they are seen to give identical results on the basis of equivalent assumptions. It is shown that it is not necessary to assume that all kinetic processes are first order and that some of the pharmacokinetic parameters may be dependent on the dose of administered drug and on the route of administration.

The introduction of statistical moments to pharmacokinetic studies by Yamaoka et al (1978) marked a significant departure from classical compartmental modelling. Their statement that "... these moments can be calculated by simple numerical integration of experimental data without a pharmacokinetic model" was perhaps to some extent responsible for this approach being described as 'model independent'. Such a description is, of course, inappropriate since no parameter estimation procedure is truly model independent. A better description is 'noncompartmental' because the methodology does not require the user to specify a full compartmental model. It is not surprising that misunderstandings have arisen (Chanter 1985; Gillespie & Veng-Pedersen 1985; Landaw & Katz 1985) as to the exact nature of the model used and the associated assumptions and restrictions. Stochastic models have been expounded by Matis et al (1983) and by Beal (1987). However, both of these papers assumed that drug molecules behave independently of each other as far as those processes which govern the pharmacokinetic behaviour of the drug are concerned. This assumption is the stochastic equivalent of the assumption that all kinetic processes are first order in deterministic models. It is not necessary to assume that all kinetic processes are first order in order to use noncompartmental methods. The purpose of this paper is to demonstrate this and to examine the modelling assumptions which are required.

The following are the parameters of interest which it is required to estimate. The fraction F, of the administered drug dose which ultimately reaches the systemic circulation is known as the systemic availability (sometimes referred to as the bioavailability). The time interval between administration and elimination (by excretion or by metabolism) from the body for a drug molecule reaching the systemic circulation is known as its residence time. The residence time is not the same for each drug molecule but has a distribution whose location may be described by its mean (MRT). Furthermore, the mean length of time the molecules reaching the systemic circulation spend in the central compartment (the plasma compartment) before elimination is denoted by MRTC. Total body clearance, $CL_T$, is defined as the ratio of the drug elimination rate and the plasma drug concentration, and is a measure of the efficiency of the elimination processes. The steady-state volume of distribution ($V_{SS}$) is considered (Gibaldi & Perrier 1982) to be the most useful parameter to describe the apparent distribution space of a drug and is defined as the ratio of the total amount of drug in the body to the drug concentration in the blood at steady-state. In the following sections expressions will be derived for these parameters which are useful for their estimation from pharmacokinetic data. Both deterministic and statistical models will be described.

The case of a single administration (by any route) of N drug molecules at a reference time ($t=0$) with n of these ultimately reaching the systemic circulation will be considered. The characteristics of the kinetic processes will be considered to be time invariant. In such circumstances F can be written,

$$F = \frac{n}{N} \tag{1}$$

## Deterministic Model

If $p(t)$ is used to denote the proportion of drug molecules reaching the systemic circulation which has a residence time of t, then

$$MRT = \int_0^\infty tp(t)dt \tag{2}$$

Let $n_e(t)$ be the number of drug molecules eliminated from the body during the time interval 0 to t. If it is assumed that all drug molecules entering the systemic circulation are ultimately eliminated then it follows that

$$n = \lim_{t\to\infty} n_e(t) \tag{3}$$

and consequently

$$F = \frac{1}{N} \lim_{t\to\infty} n_e(t) \tag{4}$$

The number of drug molecules eliminated at time t is equal to the elimination rate at time t which is the first derivative of $n_e(t)$ with respect to time. Each of the molecules eliminated at time t has a residence time of t, hence

$$p(t) = \frac{1}{n}\frac{dn_e(t)}{dt} = \frac{1}{NF}\frac{dn_e(t)}{dt} \quad (5)$$

Substituting from equation 5 into equation 2 gives

$$MRT = \frac{1}{NF}\int_0^\infty t\frac{dn_e(t)}{dt}dt \quad (6)$$

which may be integrated to give

$$MRT = \frac{1}{NF}\int_0^\infty (NF - n_e(t))dt \quad (7)$$

If it were possible to collect data relating to $n_e(t)$ then these data could be used to estimate F and the MRT without any further modelling assumptions being necessary. However, drug molecules are often excreted and metabolized via a variety of different pathways and as a result it is generally not feasible to measure $n_e(t)$, or its first derivative, directly. The quantity most easily and most often measured is the concentration of the drug in the blood at time t and this is denoted by C(t). In order to be able to use data relating to C(t) to estimate F and the MRT, the relationship between C(t) and $n_e(t)$ must be considered.

The relationship between C(t) and $n_e(t)$ may be written as

$$\frac{dn_e(t)}{dt} = CL_T N_A C(t) \quad (8)$$

where $N_A$ is Avogadro's constant and $CL_T$ may or may not be a time-dependent quantity. We will assume that total body clearance is independent of time (which implies that it is independent of dose and route of administration also). This assumption might be justified in a number of ways, one of which corresponds to a compartmental model with elimination taking place from the central compartment only by first-order processes. Integrating both sides of equation 8 with respect to time and taking limits as t approaches infinity yields

$$\lim_{t\to\infty} n_e(t) = CL_T N_A \int_0^\infty C(t)dt \quad (9)$$

Substituting from equations 8 and 9 into equations 4 and 6 gives

$$F = \frac{CL_T N_A}{N}\int_0^\infty C(t)dt = \frac{CL_T N_A}{N}AUC \quad (10)$$

$$CL_T = \frac{FN}{N_A AUC} \quad (11)$$

$$MRT = \frac{\int_0^\infty tC(t)dt}{\int_0^\infty C(t)dt} = \frac{AUMC}{AUC} \quad (12)$$

where AUC and AUMC denote the areas under the plasma drug concentration vs time curve and the corresponding first moment curve, respectively. Clearly, equations 10, 11 and 12 form a basis for the estimation of MRT and F (if $CL_T$ is known) or $CL_T$ (if F is known, e.g. F = 1 following bolus intravenous administration) from plasma drug concentration–time data.

The steady-state volume of distribution may be written as

$$V_{SS} = \frac{X_T}{C_{SS}} \quad (13)$$

where $X_T$ and $C_{SS}$ are the total amount of drug in the body and the plasma drug concentration, respectively, at steady-state, neither of which is time-dependent because of the steady-state. Now the right hand side of equation 13 can be written as

$$\frac{X_T}{C_{SS}} = \frac{CL_{Tss}}{k_{SS}} \quad (14)$$

where $CL_{Tss}$ is the total body clearance at steady-state and $k_{SS}$ is the fraction of $X_T$ eliminated per unit time at steady-state. It may be shown (for details see Appendix A) that the mean residence time at steady-state is given by

$$MRT_{SS} = \frac{1}{k_{SS}} \quad (15)$$

Hence,

$$V_{SS} = MRT_{SS} \cdot CL_{Tss} \quad (16)$$

Now, if it is reasonable to assume that following the single drug dose the MRT and $CL_T$ are equal to their steady-state equivalents and using equations 11 and 12 we can write

$$V_{SS} = \frac{FN}{N_A}\frac{AUMC}{AUC^2} \quad (17)$$

which can be used to estimate $V_{SS}$ provided F is known.

Let $n_c(t)$ be the number of drug molecules in the central compartment at time t and consider the time interval from t to t + Δt, where Δt is sufficiently small such that no drug molecules enter or leave the central compartment during the interval. Then the total time spent in the central compartment during the interval t to t + Δt is $n_c(t)\Delta t$. Allowing Δt to approach zero and summing over all such intervals gives:

the total time spent by all molecules in the central compartment =

$$\int_0^\infty n_c(t)dt \quad (18)$$

Hence,

$$MRTC = \frac{1}{n}\int_0^\infty n_c(t)dt \quad (19)$$

However,

$$n_c(t) = V_1 N_A C(t) \quad (20)$$

where $V_1$ is the volume of distribution of the central compartment and consequently we can write

$$MRTC = \frac{V_1 N_A}{NF}\int_0^\infty C(t)dt = \frac{V_1 N_A}{NF}AUC \quad (21)$$

In the case of bolus intravenous administration

$$MRTC = \frac{AUC}{C(0)} \tag{22}$$

where C(0) is the concentration of drug in the blood immediately following administration.

### Statistical Model

Assuming again that all n drug molecules reaching the systemic circulation are ultimately eliminated, their residence times $T_1, T_2, \ldots, T_n$ are random variables with a range from zero to infinity. Let the marginal probability density function (pdf) of $T_i$ be denoted by $f_{T_i}(t)$ $i = 1, 2, \ldots, n$. The numbering scheme 1, 2, ..., n by which the molecules are identified is totally arbitrary and as a consequence of this arbitrariness the molecules of drug are indistinguishable from one another. Consequently their marginal distributions must be identical, as in

$$f_{T_1}(t) = f_{T_2}(t) = \ldots = f_{T_n}(t) = f_T(t) \tag{23}$$

It is important to note that the marginal distributions being identical does not imply that they are independent of one another and no assumption regarding independence is being made here. As before

$$F = \frac{1}{N} \lim_{t \to \infty} n_e(t) \tag{24}$$

where $n_e(t)$ is the number of drug molecules eliminated from the body during the time interval 0 to t. The MRT is given by

$$MRT = \int_0^\infty t f_T(t)dt \tag{25}$$

or by

$$\begin{aligned} MRT &= \int_0^\infty u f_T(u)du \\ &= \int_0^\infty \int_0^u f_T(u)dtdu \\ &= \int_0^\infty \int_t^\infty f_T(u)dudt \\ &= \int_0^\infty (1 - F_T(t))dt \end{aligned} \tag{26}$$

where $F_T(t)$ is the cumulative distribution function (cdf) of the common marginal distribution. The probability of a drug molecule being present in the body (central or other compartment) at time t is given by $1 - F_T(t)$ which is estimated by $(NF - n_e(t))/NF$. Hence, the MRT can be estimated by

$$MRT = \frac{1}{NF} \int_0^\infty (NF - n_e(t))dt \tag{27}$$

Again we find that if it were possible to collect data relating to $n_e(t)$ they could be used to estimate F, and MRT. For the reasons cited earlier this is often not possible and the available data are blood drug concentrations denoted by C(t). We again need to model the relationship between C(t) and the elimination processes in order to be able to use C(t) data to estimate F and the MRT.

Consider a short interval of time from t to $t + \Delta t$, the probability of one or more molecules being eliminated during this interval is given by the addition law of probability as

$$P(t) = nf_T(t)\Delta t + o(\Delta t) \tag{28}$$

where $o(\Delta t)$ represents terms in $\Delta t^m$ $m \geqslant 2$. The relationship between P(t) and C(t) may be modelled as follows

$$P(t) = CL_T N_A C(t)\Delta t + o(\Delta t) \tag{29}$$

where $o(\Delta t)$ again represents terms in $\Delta t^m$ $m \geqslant 2$ and $CL_T$ is total body clearance which in the case of the statistical model is defined as the limiting value (as $\Delta t$ approaches zero) of the ratio of $P(t)/\Delta t$ to $N_A C(t)$. $CL_T$ may or may not be time dependent, we shall again consider the case where it is time independent. One way in which this might arise is if the elimination takes place from the central compartment only and the drug molecules behave independently of one another as far as the elimination processes are concerned. The derivation of equation 29 from such a model is detailed in Appendix B.

Equating the right hand sides of equations 28 and 29, dividing by $\Delta t$ and taking limits as $\Delta t$ approaches zero gives

$$nf_T(t) = CL_T N_A C(t) \tag{30}$$

Multiplying both sides of equation 30 by $t^\alpha$ and integrating with respect to t from zero to infinity gives

$$n \int_0^\infty t^\alpha f_T(t)dt = CL_T N_A \int_0^\infty t^\alpha C(t)dt \tag{31}$$

Letting $\alpha = 0$ gives

$$n = CL_T N_A \int_0^\infty C(t)dt \tag{32}$$

since $\int_0^\infty f_T(t)dt = 1$ because $f_T(t)$ is the pdf of T which takes values in the range zero to infinity. Consequently F and $CL_T$ can be written as

$$F = \frac{n}{N} = \frac{CL_T N_A}{N} \int_0^\infty C(t)dt = \frac{CL_T N_A}{N} AUC \tag{33}$$

$$CL_T = \frac{NF}{N_A AUC} \tag{34}$$

Letting $\alpha = 1$ gives

$$n \int_0^\infty t f_T(t)dt = CL_T N_A \int_0^\infty tC(t)dt \tag{35}$$

$$MRT = \frac{\int_0^\infty tC(t)dt}{\int_0^\infty C(t)dt} = \frac{AUMC}{AUC} \tag{36}$$

Using the same argument as previously and the statistical equivalent of appendix A gives

$$V_{SS} = \frac{FN}{N_A}\frac{AUMC}{AUC^2} \quad (37)$$

which can be used to estimate $V_{SS}$ if one is prepared to make the assumption that the MRT and $CL_T$ are equal to their steady-state equivalents and provided F is known e.g. following bolus intravenous drug administration.

Turning now to the residence times in the central compartment we consider, for the sake of simplicity of presentation, a situation in which each drug molecule reaching the systemic circulation makes one and only one visit to the central compartment. Let the time at which a drug molecule enters the central compartment be denoted by the random variable X and the length of time spent there be denoted by the random variable Y. Because the drug molecules are indistinguishable the joint marginal distribution of X and Y is the same for each drug molecule and since we are considering a time invariant system X and Y are independent with marginal pdf and cdf values given by $f_x(x)$, $f_y(y)$, $F_X(x)$ and $F_Y(y)$. The mean residence time in the central compartment is the mean of Y. For a drug molecule to be present in the central compartment at time t it must have entered the central compartment before t and its sojourn there must be long enough so that it is still present at time t. Hence the probability of a drug molecule being in the central compartment at time t is given by

$$P = \int_0^t \int_{t-x}^{\infty} f_x(x) f_Y(y)\,dy\,dx \quad (38)$$

$$= \int_0^t f_x(x)(1 - F_Y(t-x))\,dx \quad (39)$$

Substituting u for t − x gives

$$P = \int_0^t f_x(t-u)(1 - F_Y(u))\,du \quad (40)$$

Integrating both sides with respect to t from zero to infinity gives

$$\int_0^{\infty} P\,dt = \int_0^{\infty}\int_0^t f_x(t-u)(1 - F_Y(u))\,du\,dt \quad (41)$$

$$= \int_0^{\infty}\int_u^{\infty} f_x(t-u)(1 - F_Y(u))\,dt\,du \quad (42)$$

$$= \int_0^{\infty} (1 - F_Y(u))\{\int_u^{\infty} f_x(t-u)\,dt\}\,du \quad (43)$$

$$= \int_0^{\infty} (1 - F_Y(u))\,du \quad (44)$$

$$= MRTC \quad (45)$$

The fraction of drug molecules reaching the systemic circulation which are present in the central compartment at time t can be used to estimate *P* and as a result the MRTC can be estimated as follows

$$MRTC = \frac{1}{NF}\int_0^{\infty} n_c(t)\,dt \quad (46)$$

Again using equation 20 yields

$$MRTC = \frac{V_I N_A}{NF} AUC \quad (47)$$

The above argument can readily be generalized to the case where each drug molecule may visit the central compartment any number of times before its elimination from the body.

## Discussion

Expressions in equations 4, 6, 7, 24 and 27 were derived on the basis of a single modelling assumption that all drug molecules entering the systemic circulation are ultimately eliminated. These expressions are only useful for parameter estimation if data relating to drug elimination are available or can be collected. In the absence of such data, further modelling assumptions are required to be able to express the parameters in terms of the observable quantities. The concentration of drug in the blood stream is the most frequently observed quantity and can be related to eliminated drug by equation 8 for a deterministic model or equation 29 for a statistical model. By making the additional assumption that the total body clearance is independent of time, equations 10, 11, 12, 33, 34 and 36 were derived. This additional assumption might be justified in a number of ways and one of these corresponds to a compartmental model with elimination taking place from the central compartment only via first order processes. No assumptions regarding other pharmacokinetic processes (e.g. absorption and distribution) nor the number of kinetically distinguishable compartments were made.

Equations 17 and 37 may be used to estimate the steady-state volume of distribution, but are based on the aforementioned assumptions together with the assumption that following the administration of a single dose of drug the MRT and $CL_T$ are equal to their steady-state equivalents.

Equations 21 and 45 for the MRTC required no assumptions other than the assumption that all drug molecules entering the systemic circulation are ultimately eliminated.

It should be borne in mind that since it was not assumed that the drug molecules behave in a manner independent of one another, the parameters being estimated (other than $CL_T$) may be dependent on the dose of administered drug and on the route of administration.

## Appendix A

At steady-state the drug input and elimination rates (into and from the systemic circulation) are equal and constant as is the amount of drug in the body. Consider some reference time (t = 0); the number of drug molecules input at this time is given by $dn_e/dt$ which is the elimination rate. Let p(t) be the proportion of these 'reference' molecules which is eliminated at some time t later, then

$$MRT_{SS} = \int_0^{\infty} tp(t)\,dt \quad (A1)$$

Furthermore, the fraction of these 'reference' molecules remaining in the body up to time t which is eliminated at time t is given by

$$k_{SS} = \frac{p(t)}{1 - \int_0^t p(t)\,dt} \quad (A2)$$

where $k_{ss}$ is as defined previously. Solving equation A2 for $p(t)$ and using the solution in equation A1 gives

$$MRT_{ss} = \frac{1}{k_{ss}} \quad \text{(A3)}$$

## Appendix B

Let us assume that drug elimination takes place from the central compartment only and that each of the $n_c(t)$ drug molecules present in this compartment at time t has a probability $\lambda\Delta t$ of being eliminated during the interval t to $t + \Delta t$, where $\lambda$ is a constant. If it is further assumed that as far as the elimination processes are concerned the drug molecules behave independently of one another, then the probability of r drug molecules being eliminated during the interval t to $t + \Delta t$ is given by the binomial probability.

$$Pr(\text{r eliminated}) = \binom{n_c(t)}{r} (\lambda\Delta t)^r (1 - \lambda\Delta t)^{n_c(t)-r} \quad \text{(B1)}$$

Hence the probability of one or more molecules being eliminated during the interval t to $t + \Delta t$ is

$$P(t) = 1 - (1 - \lambda\Delta t)^{n_c(t)} \quad \text{(B2)}$$

Which gives

$$P(t) = n_c(t)\lambda\Delta t + o(\Delta t) \quad \text{(B3)}$$

where $o(\Delta t)$ represents terms in $\Delta t^m$ $m \geqslant 2$.

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