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A CLOSER LOOK AT THE MEAN RESIDENCE TIME (MRT) CONCEPT BASED ON STATISTICAL MOMENTS

Umesh V. Banakar

Creighton University
School of Pharmacy & Allied Health Professions
Omaha, NE 68178.
U.S.A.

ABSTRACT

Mean Residence Time (MRT) based on statistical moments, presuming the residence time of drug in a system to be in congruence with a frequency distribution curve, can give reliable estimate of true MRT only for monoexponential distributions (one-compartment models). However, significantly erroneous results are obtained for the frequently observed biexponential (two-compartment models) distributions. There is a definite need for reassessment of this increasingly popular concept, particularly focussing on this conceptual misunderstanding, in view of its true potential and applicability.

INTRODUCTION

Statistical moments have been extensively employed for data analysis in chemical engineering (1). One of the earliest applications to biological systems was provided in a report concerned with the kinetics of body cholesterol in man (2). The application of statistical concept of moments to pharmacokinetics was virtually simultaneously reported (3,4). Since then statistical moments have become increasingly popular and have

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been widely employed in different areas of bioavailability determinations, in vivo-in vitro correlations in particular.

The theory of statistical moments is based on the preliminary assumption that the movement of the individual drug molecules through a body compartment is governed by probability. Furthermore, "the time course of drug concentrations in plasma can usually be regarded as a statistical distribution curve (3). Thus the residence time of the drug in the body can be conceived as a frequency distribution with the mean and variance about the mean (5). However, on a closer examination, this curve is not a statistical distribution curve. It is the intention of this paper to explore the impact this invalid assumption has on the application capability of this theory. In the process an attempt is made to focus on the conceptual misunderstanding of the Mean Residence Time (MRT) based on statistical moments.

METHODOLOGY

In order to exemplify the aforementioned objective, it will be appropriate to start with the conventional theory currently in use.

The Mean Time as defined by Dost (6) is "the statistical mean of all particular times any individual molecule of a dose is held up within a pharmacokinetic system prior to being eliminated from it." Consequently, it encompasses all pharmacokinetic processes, including in vivo drug release from dosage form, absorption in to the body and all disposition processes. The MRT can be simplistically derived and stated as follows :

$$AUC_0^\infty = \int_0^\infty Cp.dt \qquad (1)$$

and

$$AUMC_0^{\infty} = \int_0^{\infty} t.Cp.dt \qquad (2)$$

$$MRT = AUMC_0^{\infty} / AUC_0^{\infty} \qquad (3)$$

where, Cp is the concentration of drug in plasma at any time, t, and AUC_0^{∞} (zero moment) is the area under the concentration-time curve t=0 to t=∞ . $AUMC_0^{\infty}$ (First moment) is the area under the curve of the product of time, t, and plasma concentration, Cp from t=0 to t= ∞. MRT is the Mean Residence Time originally defined for instantaneous input e.g., IV, but now generalized for noninstantaneous input as well (3).

This theory is usually attested with a disclaimer statement to the effect that it is only applicable to linear systems where all processes involved follow first-order kinetics. As a result, these processes when translated into first order kinetics lead to a drug-concentration-time-curve being a sum total of exponential terms, such as :

$$C = \sum_i C_i . e^{-\alpha_i.t} \qquad (4)$$

The relationship between the statistical distribution of residence times and MRT can be clarified on consideration of non-linear systems with instantaneous input in the first case and non-instantaneous input in the second case.

First, lets consider a hypothetical situation where there is an instantaneous input of drug (say at concentration C') in the system. Furthermore, lets assume that all of the drug molecules reside in and are eliminated from the system at the same time ,T. It is apparent that the MRT in this case must be T. On applying conventional theory to this situation the following can be derived :

$$AUC_0^{\infty} = \int_0^{T} C'.dt = C'.T \qquad (5)$$

and

$$AUMC_0^{\infty} = \int_0^T t.C'\,dt = 0.5\ C'.T \quad (6)$$

Therefore, $MRT = 0.5\ T$ (7)

The discrepency is obvious. The reason for this discrepency can be attributed to the fact that the statistical distribution of residence times (expressed as a histogram) would be only one column as shown in Fig. 1. However, this is unrealistic for drug-concentration curve. Realistically it would be a rectangle as depicted in Fig. 2. Nevertheless, if Eqn. 2 is applied then the correct result is obtained.

On this premise, it would be all the more logical to evaluate a system which leads to exponential concentration-time curves which are more realistic and confronted with routinely. But, the first step is to examine and explain the relationship between the true statistical distribution of the residence time of the molecules of a dose of drug and the biological time curve resultant therefrom.

Let us consider a pharmacokinetic system where a drug is given instantaneously and the elimination occurs via central compartment. Assume that the drug molecules heve a residence time which follows a statistical distribution, f(T). Then the probability density function, f(T) will describe the probability of a randomly chosen molecule remaining in the system for a time, t, before being eliminated. The prerequisite being $P(o<t<\infty)=1$. Therefore,

$$P(X<t<Y) = \int_0^{\infty} f(T).dt \quad (8)$$

It is well recognized that drug concentration in plasma at any time, t, will be equal to that proportion of the initial concentration which remains to be eliminated at that time, t. Thus,

$$Cp = (Cp)_0 \int_t^{\infty} f(t).dt \quad (9)$$

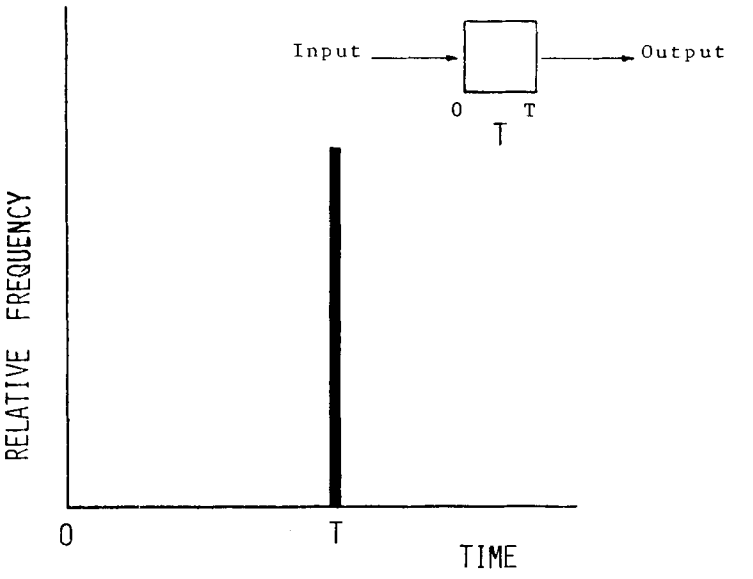

Fig. 1. Relative Frequency as a Function of Residence Time for a Model where all the Molecules of the Drug Reside in and are Eliminated at the same Time (T).

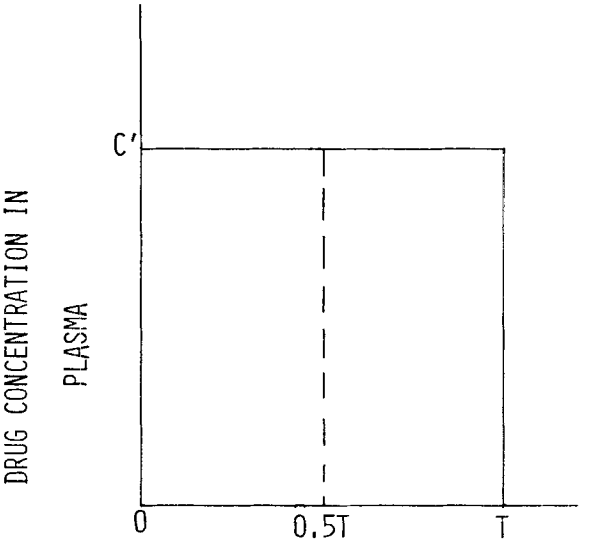

Fig. 2. Plasma-Drug-Concentration as a Function of Time Following Instantaneous Input and Elimination at the same Time. Note 0.5T is the MRT resultant of the Application of the Statistical Moment Theory.

When the statistical distribution of the residence times is an exponential distribution, then

$$f(T) = A.e^{-\alpha \cdot t} \quad (10)$$

The plasma-drug-concentration-time-curve will be :

$$Cp = (Cp)_o .e^{-\alpha \cdot t} \quad (11)$$

Except for the coefficient of the equation, Eqns. 10 and 11 are identical. Consequently, if we apply the statistical moments technique or Eqn. 11 we will get the same result for MRT,

$$MRT = 1/\alpha \quad (12)$$

It must be noted that in the latter we are assuming $Cp=(Cp)_o \cdot e^{-\alpha \cdot t}$ can be treated as probability density function whereas, in the former it would be the correct application of the technique. Evidently, only in cases where drug-concentration-time data that can be decidedly fitted with monoexponential function, statistical moments can estimate MRT within reasonable limits of reliability.

Analogous to the previous discussion, in case of statistical distribution resultant of a conglomerate of two exponential distributions, the probability density function can be stated as follows :

$$f(T) = l.A.e^{-\alpha \cdot t} + m.B.e^{-\beta \cdot t} \quad (13)$$

where, l and m are conglomerate fractions such that l+m = 1 in order to be in congruence with the requirements of Eqn. 8. Equation 13 is the true statistical distribution. On application of statistical moments to Eqn. 13 :

$$MRT = l/\alpha + m/\beta \quad (14)$$

Drug concentration-time data which can be fitted with biexponential model can be expressed as :

$$Cp = (Cp)_o .[\, l.e^{-\alpha \cdot t} + m.e^{-\beta \cdot t} \,] \quad (15)$$

or

$$Cp = A.e^{-\alpha \cdot t} + B.e^{-\beta \cdot t} \qquad (15a)$$

Applying statistical moments technique to Eqn. 15 assuming it to be a statistical distribution, then

$$MRT = [1/(\alpha)^2 + m/(\beta)^2]/[1/\alpha + m/\beta] \qquad (16)$$

The net result (MRT determinations on employment of Eqn. 16 and Eqn. 14) will be identical if and only if $\alpha = \beta$, where it will be transformed into a single exponential expression. Additionally, this will be true only when l or m will be equal to zero.

In order to test the impact of this theory, data reported by Park (7) during investigation of I.V. pharmacokinetics and oral bioavailability of amrinone in humans was employed. Park and his co-workers reported that the plasma data during IV phase could be described by open two-compartment body model as :

$$Cp = 4.62\ e^{-8.94 \cdot t} + 0.64\ e^{-0.19 \cdot t}$$

The various parameters (employing this expression) will be : $\alpha = 8.94(h^{-1})$, $\beta = 0.19(h^{-1})$, A=4.62 mcg/mL, B=0.64 mcg/mL, l=0.8783 and m=0.1217. Employment of Eqn. 14 gives MRT = 0.74 h whereas, on employing Eqn. 16 the MRT = 4.57 h. There is marked difference in the results.

In order to demonstrate that MRTs calculated using Eqns. 14 and 16 will equal only when α approaches β or vice-versa, the β values were changed arbitrarily while α was held constant. Subsequently, the MRT values were determined using Eqns. 14 and 16 for each of the chosen value of β. The results are shown in Table 1.

Von Hattingberg and Brockmeier (8) have suggested an alternative method. They reported that MRT can be calculated from Eqn. 17 on the assumption that the elimination of the drug takes place only from the central compartment.

$$MRT = AUC/C_0 \qquad (17)$$

TABLE 1

MRT Values Computed using Eqns. 14 and 16 Resultant to Changes in α while maintaining $\beta = 8.94\ h^{-1}$.

β h^{-1}	Computed MRT (h) values Using		% Difference
	Eqn. 14	Eqn. 16	
0.19	0.74	4.57	83.8
1	0.22	0.60	63.3
3	0.14	0.18	22.2
5	0.12	0.13	7.7
7	0.12	0.12	0
8.94	0.11	0.11	0

* Value as reported by Park et al., (7).

However, with this constraint the MRT for a system with instantaneous input can be determined simply from the knowledge of AUC and initial concentration, C_0. Consequently, this method provides very limited information than that contained in the AUC. Additionally, this method is not truely model independent.

CONCLUSIONS

In conclusion, it is clear that the MRT concept based on statistical moments can be applied only with reservations. The above discussion is not intended to undermine the applicability of the theory but to caution the user of its limitations. This parameter (MRT) can be employed as a means towards drawing definitive conclusions rather than vice-versa. There is a need for rigorous reevaluation of this concept in view of its true potential and applicability.

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