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Letter to the Editor

Mean residence time: an invalid estimation method

ADRIAN DUNNE, DAVID H. WILLIAMS, *Department of Statistics, University College Dublin, Belfield, Dublin 4, Ireland*

The mean residence time (MRT) has become a widely reported pharmacokinetic parameter. Misunderstandings have arisen (Chanter 1985) as to how it should be computed and under what circumstances the computations are valid. The purpose of this note is to point out a misinterpretation of one of the properties of the MRT and the consequent invalidity of a method for its estimation based on the incorrect interpretation.

The time interval between the introduction of a drug molecule into the body and its elimination (excretion or metabolism) from the body is known as its residence time. Generally a large number of molecules are administered together and their residence times are not all equal but are randomly distributed over some time range. Because of this random behaviour, statistical terminology and methods are appropriate for the description of residence times. The location of a statistical distribution is usually described by the mean which is the arithmetic average of all values.

Riegelman & Collier (1980) stated that when the residence time is log-normally distributed, "... the MRT represents the time for 63·2% of the administered dose to be eliminated by all processes. Thus one might use (accurately determined) accumulative urinary excretion data to estimate the MRT". It is not generally true that 63·2% of log-normally distributed values are less than or equal to the mean as can be seen from the following:

Let the residence time be represented by a random variable X. Consider a situation in which X is log-normally distributed with mean μ and variance σ^2. The probability density function of X can be written as

$$f(x) = \frac{1}{x\theta\sqrt{2\pi}} \exp\left(-\frac{1}{2}\left(\frac{\ln x - \phi}{\theta}\right)^2\right) \qquad x \geq 0 \qquad (1)$$

where

$$\theta = \sqrt{\ln\left(1 + \frac{\sigma^2}{\mu^2}\right)} \quad \text{and} \quad \phi = \ln\left(\frac{\mu^2}{\sqrt{\mu^2 + \sigma^2}}\right) \qquad (2)$$

which can also be written as

$$\mu = e^{\phi + \frac{1}{2}\theta^2} \quad \text{and} \quad \sigma^2 = e^{2\phi + \theta^2}(e^{\theta^2} - 1) \qquad (3)$$

Transform X to Y where

$$Y = \ln X \qquad (4)$$

then Y is normally distributed with mean ϕ and variance θ^2. The probability of X taking a value less than or equal to μ is given by

$$\begin{aligned} P(X \leq \mu) &= P(Y \leq \ln \mu) \\ &= P(Y \leq \phi + \tfrac{1}{2}\theta^2) \\ &= P\left(\frac{Y - \phi}{\theta} \leq \tfrac{1}{2}\theta\right) \end{aligned} \qquad (5)$$

This probability depends on the value of θ and can be read from the tabulated standard normal distribution when the value of θ is known. The fraction of values less than or equal to μ is 63·2% only in the special case where $\theta = \frac{2}{3}$, i.e. when the standard deviation of the distribution of Y is $\frac{2}{3}$. This condition can be expressed in terms of the distribution of X. Equation (3) gives

$$\sigma^2 = \mu^2(e^{\theta^2} - 1) \qquad (6)$$

Therefore when $\theta = \frac{2}{3}$ then

$$\sigma = 0{\cdot}748\,\mu \qquad (7)$$

Hence 63·2% of log-normally distributed residence times are less than equal to the MRT if and only if the standard deviation of the residence time is equal to 0·748 times the MRT. It must be emphasised that the above discussion only applies to log-normally distributed residence times.

Gibaldi & Perrier (1982) have stated that following bolus intravenous administration 63·2% of the residence times are less than or equal to the MRT irrespective of the distribution characteristics of the drug. The distribution characteristics of the drug determine the statistical distribution of the residence times, consequently their statement is equivalent to saying that 63·2% of the residence times are less than or equal to the MRT irrespective of the residence time distribution. This is clearly erroneous since it is not true in the case of a symmetrical distribution (where the value is 50%) nor is it generally true in the case of the log-normal distribution as shown above. This conclusion is in accord with that of Weiss (1988).

In general then it is not valid to estimate the MRT as the time required to eliminate (by urinary excretion or otherwise) 63·2% of the administered dose (or of that amount of the dose which is ultimately excreted in the urine).

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Correspondence to: A. Dunne, Department of Statistics, University College Dublin, Belfield, Dublin 4, Ireland.

References

Chanter, D. O. (1985) The determination of mean residence times using statistical moments: is it correct? J. Pharmacokin. Biopharm. 13: 93–100

Gibaldi, M., Perrier, D. (1982) Pharmacokinetics, Marcel Dekker, New York, pp 412

Riegelman, S., Collier, P. (1980) The application of statistical moment theory to the evaluation of in vivo dissolution time and absorption time. J. Pharmacokin. Biopharm. 8: 509–534

Weiss, M. (1988) Washout time versus mean residence time. Pharmazie 43: 126–127