SCIENTIFIC COMMENTARY

The Application of Statistical Moment Theory to the Evaluation of in vivo Dissolution Time and Absorption Time

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Moments analysis has been applied to the calculation of mean (in vivo) dissolution time (MDT) and mean absorption time (MAT) from plasma level of drug versus time data. Methods for accurately estimating the MDT under varying conditions, limitations of the methods, and interpretation of the data are presented. The importance of accurate estimates of the terminal rate constant \( \lambda_\infty \) and the drug concentration at the time of withdrawing the final plasma sample \( C_f \) is emphasized in connection with extrapolation to \( t = \infty \). The appropriate use of a logarithmic trapezoidal equation for calculating the area under the moments curve (AUMC) is shown to increase the accuracy of estimating MDT.

KEY WORDS: mean dissolution time in vivo; MRT; MAT; moments; bioequivalence.

INTRODUCTION

The application of the statistical concept of moments to pharmacokinetics was virtually simultaneously reported in 1979 by Yamaoka et al. (1) and Cutler (2). This concept has many significant applications in pharmacokinetic calculations, particularly in the area of estimation of the time involved in the in vivo release and absorption processes. The purpose of this commentary is to review and clarify these concepts, their methods of calculation, and to expand upon their potential utility.

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Drug transit through the body is a stochastic process. The term "stochastic" is derived from the Greek word related to a target. When a series of shots are aimed at a target, most will not hit the exact center. Because of the implied random scatter around a general cluster, the word has become established in the vocabulary of probability theory and statistics. The movement of individual molecules through a body compartment is governed by probability, since they will not all be metabolized or excreted at the same time. 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. Analysis of the distribution function can be made by the use of the method of moments. In this procedure, the standard deviation (variance), skewness, and kurtosis of the distribution can be estimated by calculation of the first to fourth moments of the distribution (3).

In pharmacokinetics, we have regularly utilized measurement of the area under the concentration time curve from zero time to infinity (AUC∞). The area under the first moment of the curve is defined as the area under the curve of the product of time, t, and plasma concentration, Cp, from zero time to infinity and was referred to by Benet and Galeazzi (4) as the area under the (first) moment curve AUMC∞; thus

$$AUC_{\infty} = \int_{0}^{\infty} Cp \, dt$$

and

$$AUMC_{\infty} = \int_{0}^{\infty} tCp \, dt$$

Perl and Samuel (5) and Oppenheimer et al. (6) defined the mean residence time (MRT) as follows:

$$MRT = \frac{\int_{0}^{\infty} tCp \, dt}{\int_{0}^{\infty} Cp \, dt} = \frac{AUMC_{\infty}}{AUC_{\infty}}$$

While originally defined for intravenous (instantaneous) input, in the chemical engineering literature (7), the concept was generalized to noninstantaneous inputs, and this approach was applied by Yamaoka et al. (1). The mean residence time can therefore be defined as the mean time for the intact drug molecules to transit through the body and involves a