The Cutoff Time Point of the Partial Area Method for Assessment of Rate of Absorption in Bioequivalence Studies

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Received August 5, 1993; accepted January 4, 1994

The partial area method has been suggested for the assessment of the absorption rate in bioequivalence studies. This paper provides a theoretical basis for the estimation of the optimal cutoff time point of the partial areas for drugs with one compartment model disposition. The analysis is performed by using the appropriate equations which relate the normalized (in terms of the extent of absorption) partial areas with time expressed in terms of multiples of half-life. Provided that the quality of experimental data ensures precise estimation of the parameters, the t_{max} of the formulation with the faster absorption characteristics is generally the most practical cutoff time point for calculation of the normalized partial areas, when a drug follows one compartment model disposition with linear absorption.

KEY WORDS: partial area method; bioequivalence; absorption rate; cutoff time.

INTRODUCTION

For absorption rate assessment in bioequivalence studies, one should obtain the plots of the cumulative amount of drug absorbed versus time for the test and the reference formulation and compare instantaneous rates of absorption from the slopes of these plots. However, this procedure is impractical. One way to overcome this difficulty is to find a parameter which is not dependent on the extent of absorption using either compartmental or non-compartmental approaches. The absorption rate constant represents a good absorption rate indicator if the former approach is utilized. Experimental values for C_{max} and t_{max} have been traditionally used as non-compartmental absorption rate indicators. However, their validity has been consistently criticized and alternative metrics have been proposed recently [1-3].

Chen[4] proposed the non-compartmental partial area method for the assessment of rate of absorption of immediate release formulations in bioequivalence studies. This method was found to be more discriminating than C_{max} and/or t_{max} in the evaluation of the absorption rate of drugs. A crucial parameter of the method is the cutoff time point for partial area under the curve, AUC_{0-t}, calculations. According to Chen[4], the cutoff time point may vary with the type of drug under study, depending on its clinical use and onset of action.

The use of partial areas as indicators of the rate of absorption has also been suggested previously. Based on simulated data, Rosenbaum et al[5] found that, when the rate of absorption was the only difference between a test and a reference formulation, the ratio of the areas under the curve (test to reference) was essentially 1.0 by the time at which 40% of the area was characterized in the one-compartment model and 60% was characterized in the two-compartment model. However, the incremental AUC representing less than 40% or 60% of the area under the curve from time zero to infinity, $AUC_{0-\infty}$, for one or two compartment model, respectively, was actually found to be a better indicator of the absorption rate difference than either C_{max} or t_{max}.[5]

The present study was undertaken in order to explore the theoretical basis of the partial area method for the assessment of rate of absorption in bioequivalence studies by addressing the question about the optimal time point for the calculation of partial areas.

THEORY

Our analysis was based on the assumption that both formulations (reference and test) obey one-compartment model kinetics with linear absorption. It has been recently shown[6] that the following equation is valid for a drug following one compartment model disposition kinetics with first order absorption:

$$\frac{AUC_{0\text{-}nt1/2}}{AUC_{0-\infty}} = 1 - \frac{\phi(0.5)^n - (0.5)^{n\phi}}{\phi - 1} \qquad (1)$$

where n is a dimensionless positive number expressing time in multiples of elimination half-life, $t_{1/2}$, ϕ is the ratio of absorption rate constant, k_a, and the elimination rate constant, k_{el}, and $AUC_{0\text{-}nt1/2}$ is the area under the curve from time zero to $t = nt_{1/2}$. Equation 1 reveals that the partial area normalized in terms of the extent of absorption is a kinetic parameter. Conceivably, the ratio of AUCs presented in equation 1 could be also used to evaluate formulation differences in the rate of drug absorption.

Equation 2 describes the ratio of the areas for the reference formulation (R):

$$\frac{AUC_{0\text{-}nt1/2,R}}{AUC_{0-\infty,R}} = 1 - \frac{\phi_R(0.5)^n - (0.5)^{n\phi_R}}{\phi_R - 1} \qquad (2)$$

where ϕ_R is the ratio of the rate constants of the reference formulation i.e. $\phi_R = k_{a,R}/k_{el,R}$. The corresponding equation for the test formulation (T) can be written as follows:

$$\frac{AUC_{0\text{-}nt1/2,T}}{AUC_{0-\infty,T}} = 1 - \frac{m\phi_R(0.5)^n - (0.5)^{nm\phi_R}}{m\phi_R - 1} \qquad (3)$$

with $m = \phi_T/\phi_R$, and ϕ_T the ratio of the rate constants of the test formulation. Assuming that both the reference and the test formulations exhibit the same elimination characteristics (i.e., $k_{el,R} = k_{el,T}$) the value of m corresponds to the ratio of the absorption rate constants of the two formulations, i.e. $m = k_{a,T}/k_{a,R}$.

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0724-8741/94/0600-0831$07.00/0

By subtracting equations 2 and 3 it can be obtained:

$$\Delta = \frac{AUC_{0\text{-}ntl/2,T}}{AUC_{0\text{-}\infty,T}} - \frac{AUC_{0\text{-}ntl/2,R}}{AUC_{0\text{-}\infty,R}} = \frac{\phi_R(0.5)^n - (0.5)^{n\phi_R}}{\phi_R - 1} - \frac{m\phi_R(0.5)^n - (0.5)^{nm\phi_R}}{m\phi_R - 1} \quad (4)$$

Equation 4 gives the difference of partial areas normalized for the extent of absorption with the cutoff time point expressed in terms of multiples of elimination half life.

However, since the quotient of AUCs is commonly used in bioequivalence studies, by following a similar procedure the quotient of the $AUC_{0\text{-}t}$s can be written by dividing equation 3 by equation 2:

$$Q = \frac{AUC_{0\text{-}ntl/2,T}/AUC_{0\text{-}\infty,T}}{AUC_{0\text{-}ntl/2,R}/AUC_{0\text{-}\infty,R}} = \frac{1 - \dfrac{m\phi_R(0.5)^n - (0.5)^{nm\phi_R}}{m\phi_R - 1}}{1 - \dfrac{\phi_R(0.5)^n - (0.5)^{n\phi_R}}{\phi_R - 1}} \quad (5)$$

Equation 5 gives the quotient of partial areas normalized for the extent of absorption with the cutoff time point expressed in terms of multiples of elimination half life.

RESULTS AND DISCUSSION

The comparison of the absorption rates in bioequivalence studies could be based on the difference of the normalized partial AUCs. The critical cutoff point can theoretically be evaluated by plotting the difference of normalized partial areas as a function of n. Figure 1 shows a plot of the left-hand side of equation 4 versus n for various values of ϕ_R. In this Figure the value of m (i.e. the ratio of k_as of the two formulations) has been assigned 1.2. It is seen that the magnitude of the difference depends on the value of n, i.e. the cutoff point chosen. Regardless of the value of ϕ_R, the absolute difference of the normalized partial areas reaches a maximum. The larger the value of ϕ_R (immediate release formulation) the smaller the magnitude of n which corresponds to the maximum value of the absolute difference of the partial areas. Moreover, this peak difference in the partial areas is larger for the slow release formulations (i.e. low values of ϕ_R). The values of n (designated as n*), which correspond to the maxima of the curves of Figure 1, can be calculated by equating with zero the first derivative of equation 4 and solving the resulting equation 6:

$$\phi_R \ln(0.5)\left\{\frac{m}{m\phi_R - 1}[(0.5)^n - (0.5)^{nm\phi_R}] - \frac{1}{\phi_R - 1}[(0.5)^n - (0.5)^{n\phi_R}]\right\} = 0 \quad (6)$$

Equation 6 is solved with numerical iteration using various values for m and ϕ_R. Figure 2 shows a plot of n* (in essence, time for maximum difference in the partial areas) versus m for various values of ϕ_R. The effect of m on the value of n* becomes more pronounced as ϕ_R decreases. Although Figure 2 has a universal applicability since both axes are dimensionless, a more realistic analysis can be based on the values of the actual time, t*, at which the maximum difference occurs. This time will obviously be a function of n* and will be related to t_{max} as follows[7]:

$$t^* = n^* t_{1/2} = n^* \frac{\ln 2}{k_{el}} = n^* \frac{t_{max}(\phi - 1)}{\ln\phi} \ln 2 \quad \text{therefore}$$

$$t^*/t_{max} = n^* \frac{(\phi - 1)\ln 2}{\ln\phi} \quad (7)$$

Equation 7 can be applied by using the t_{max} of the reference formulation (i.e. $t_{max} = t_{max,R}$, and therefore $\phi = \phi_R$) or the t_{max} of the test formulation (i.e. $t_{max} = t_{max,T}$, and therefore $\phi = m\phi_R$). The values of n* were calculated for various values of m from equation 5. Analysis of the data showed

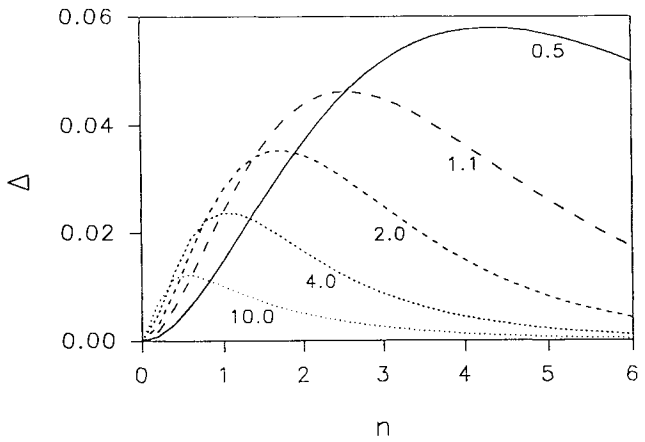

Figure 1: Plot of the absolute difference of the normalized partial areas of the test and reference formulations, Δ, as a function of multiples of elimination half-life, n, for various values of the ratio $k_{a,R}/k_{el}$ ranging from 0.5 to 10.0. The value of the ratio $k_{a,T}/k_{a,R}$ is always 1.2.

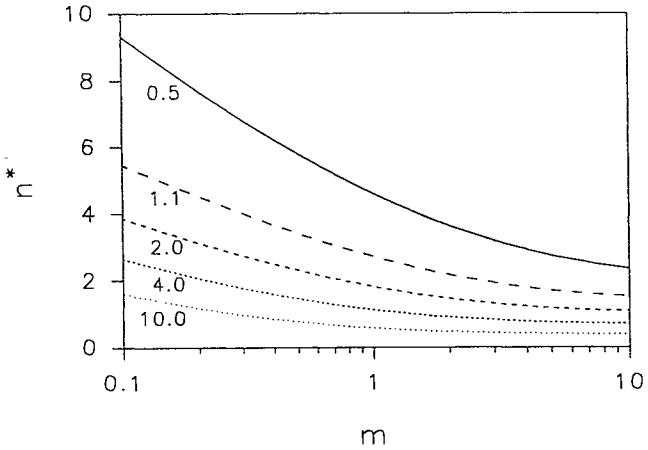

Figure 2: Plot of multiples of elimination half life at which the maximum absolute difference of the partial areas of the formulations occurs, n*, as a function of the ratio of absorption rate constants, m = $k_{a,T}/k_{a,R}$, for various values of the ratio $k_{a,R}/k_{el}$ ranging from 0.5 to 10.

that the time for the maximum difference of partial areas occurs always later than t_{max}. Also, the more the m deviates from unity, the more the value of t* approaches the t_{max} of the formulation with the longer t_{max}. Further, the maximum difference of partial areas increases as the value of ϕ_R decreases or the value of m deviates from 1.

The aforementioned analysis was based on the absolute difference of the normalized partial areas. However, in bioequivalence testing it is the relative difference that is mostly required to be assessed, and, as a rule of thumb, this difference should be less than 20% of the reference mean for approving bioequivalence. This relative difference of the partial areas (which in reality represents the ratio of test versus reference formulation), in contrast to the absolute difference, shows no maxima or minima but it is monotonically decreasing as a function of n. To acquire an insight of the relationship of the ratio of partial areas, Q, with n, equation 5 was used. Figure 3 shows how Q varies with n for various values of ϕ_R using a representative value for m (m = 1.2). In contrast to the absolute differences of the partial areas (Figure 1), Q is monotonically decreasing as n increases. The magnitude of the decrease depends on ϕ_R, and m. For m>1 the curve is declining and asymptotically approaching the unity (Figure 3). Obviously, for m<1 the curve (not shown) is continuously increasing and approaching the unity. Regardless of the value of m, the earlier a time point is chosen the more the ratio, Q, at this time point deviates from unity. In practice, however, it is inconvenient and unreliable to calculate partial areas using only the earliest data points of the absorption phase. Consequently, a practical cutoff time point for the calculation of the partial areas could be the t_{max}. Conceivably, it is better (from the sensitivity point of view) to choose the t_{max} of the reference formulation, $t_{max,R}$, when m<1 and the t_{max} of the test formulation, $t_{max,T}$, when m>1, i.e. the shortest t_{max}. This conclusion is substantiated with Figure 4 where Q is plotted against m for various values of ϕ_R. Figures 4a and 4b show that, when m<1, Q calculated at $t_{max,R}$ is more sensitive than Q calculated at $t_{max,T}$; the opposite is observed when m>1. It is

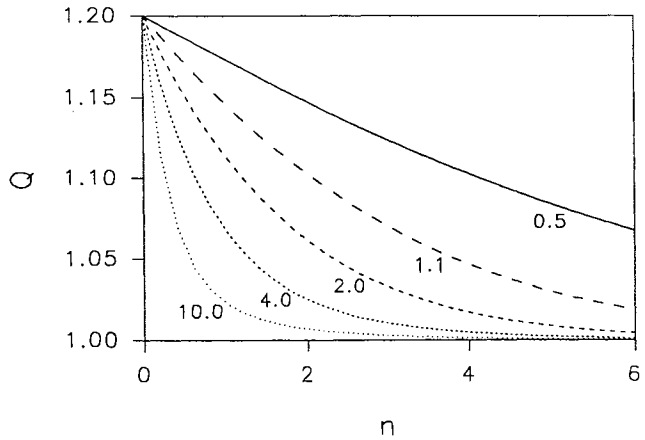

Figure 3: Plot of the ratio of the normalized partial areas, Q, as a function of multiples of elimination half life, n, for various values of the ratio $k_{a,R}/k_{el}$ ranging from 0.5 to 10.0. m is constant and equal to 1.2 in all cases.

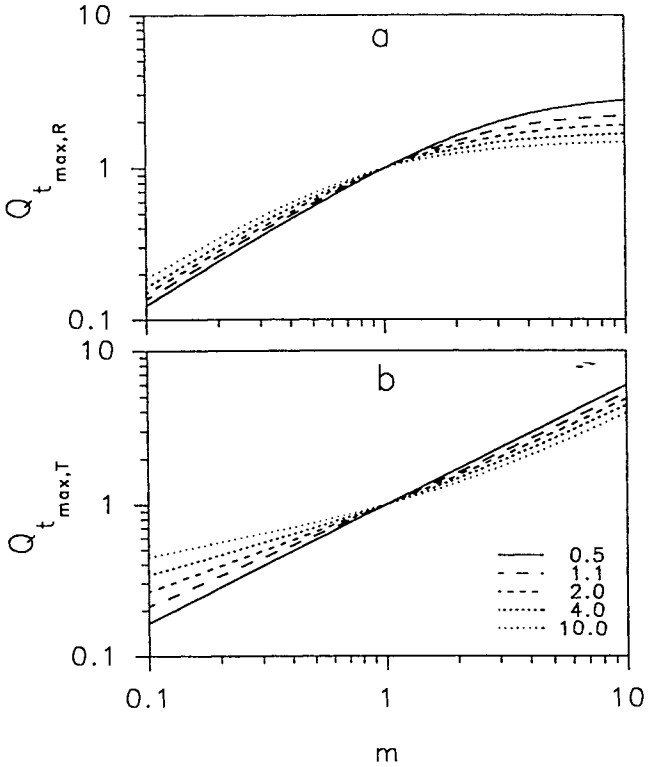

Figure 4: Plot of the ratio of the normalized partial areas at $t_{max,R}$ (a) and at $t_{max,T}$ (b) as a function of m for various values of the ratio $k_{a,R}/k_{el}$, ranging from 0.5 to 10.0.

interesting to note that a similar remark has been pointed out by Chen[4] following a totally different approach. However, as Chen has also suggested[4], the statistical or decisional criteria of ±20% may have to be relaxed.

In conclusion, normalized partial areas could, in principle, be used as absorption rate indicators in bioequivalence studies since any effect of the extent of absorption is eliminated. In the case of drugs with one compartment model disposition and linear absorption, the optimal cutoff time point (common for both formulations) would be the t_{max} of the formulation with the faster absorption characteristics. However, it is clear, that the applicability of normalized partial areas as absorption rate indicators needs to be further tested with data which simulate various scenarios of the real situation. The precision of estimation of partial areas in bioequivalence studies is expected to be limited by

—factors which affect the ability to define the true t_{max}, i.e. the sharpness of the apex of the concentration-time profile, and the frequency of sampling in the region of the peak of the curve,

—the precision of the plasma concentration levels measurement,

—the existence of multiple peaks on the concentration-time profile, and

—variable delays in absorption (i.e. variable lag time) in conjunction with the quantification limit of the assay.

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