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Research Article

An Alternative Approach for Assessment of Rate of Absorption in Bioequivalence Studies

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The partial area method was investigated for evaluation of equivalency in the rate of absorption of immediate release formulations. The applicability of the method was demonstrated with four drugs with different pharmacokinetic/pharmacodynamic characteristics. The confidence interval approach currently employed for bioequivalence determinations was applied to the relevant absorption parameters, including C_{max} and partial AUCs. The method was found to be more discriminating than C_{max} and/or T_{max} in the evaluation of the absorption rate of drugs. The cutoff time or point for partial AUC calculation may vary with the type of drug under study, depending on its clinical use and onset of action. The method was shown to be useful in the assessment of rate of absorption in bioequivalence studies.

KEY WORDS: bioequivalence; absorption rate; partial AUC; truncated AUC; peak concentration; time to peak.

INTRODUCTION

Concerns have been raised with respect to the assessment of rate of absorption for drugs in bioavailability studies and bioequivalence evaluations (1–6).

Currently, the Food and Drug Administration (FDA) evaluates rate of drug absorption by the peak concentration (C_{max}) and time to peak (T_{max}) obtained from plasma/serum concentration–time profiles. The utilization of C_{max} and T_{max} as a measure of rate of absorption has been criticized in many ways (1–3,5,6). The C_{max} and T_{max} contain minimal information about the absorption rate and absorption process for the drug. In practice, these parameters are determined experimentally and, as such, depend heavily upon the sampling time schedule. These parameters are not well defined in the presence of multiple peaks or when the plasma concentration curve around the peak is flat. Above all, due to the lack of statistical methods for T_{max} comparisons, C_{max} becomes the only parameter used for estimation of absorption rate in most cases, which appears to be inappropriate for bioequivalence assessment.

The applicability of moment analysis in the estimation of rate of absorption has been examined previously (2). Mean absorption time (MAT) may be employed for assessing equivalency when used in conjunction with C_{max}. However, the application of MAT in bioequivalence determination is limited by the fact that the relative error increases with the ratio of MRT/MAT (where MRT is the mean residence time, a variable needed for the calculation of MAT). In some situations, the error involved is so substantial that negative values of MAT may result for drugs under this category.

Literally, the absorption rate of the drug is a continuous varying function with the dimensions of mass (or amount) per unit time. With the exception of zero-order absorption processes, the input rate can be defined only at a particular time, t, which can be obtained from the slope of the plot of cumulative amount of drug absorbed vs time. In principle, for bioequivalency assessment, one can obtain similar plots for two formulations of a drug and the comparison of *instantaneous* rates of absorption can be made from the slope(s) of the plots. Obviously, this procedure is impractical and unrealistic in its application to bioequivalence studies.

When the absorption kinetics are of interest, profiles exhibiting the time dependence of absorption rate would be most informative. However, the application of absorption profiles in rate evaluation for bioequivalence studies is limited due to a variety of difficulties in the construction of absorption profiles, as well as the lack of statistical criteria for profile comparisons in bioequivalence assessment (6). In the event that the absorption kinetics are not so much desired as the prominent absorption rate, an estimation of the average rate of absorption over the absorption phase would suffice to provide an insight into the absorption process. The plasma/serum concentration–time curve of a drug can be perceived as a time course of drug absorption, distribution, metabolism and excretion. For immediate release formulations, in most cases, the absorption process takes place within a short time span and is nearly complete when the plasma/serum drug level reaches its peak. Conceivably, drug level curves in the early phase after dosing may shed some light on the absorption rate of the drug. In this respect, the preliminary observation of Rosenbaum *et al.* (7) has indi-

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cated that the incremental area under the drug level curve (AUC) representing 10–30% of the total AUC would be more sensitive than either C_{max} or T_{max} in differentiating formulation differences in the rate of absorption of the drug.

The purpose of this paper is (i) to investigate the characteristics of the "partial area method" in the assessment of absorption rate of drugs and (ii) to explore the feasibility of the proposed method as a means of rate comparison in bioequivalence evaluations.

METHODS

In an effort to test the applicability of the "partial area method" in bioequivalence evaluations, the proposed method was applied to the data collected from bioequivalence studies. For illustration purposes, four drugs with differing absorption kinetics and/or pharmacokinetics/pharmacodynamics have been chosen, including cephradine, ibuprofen, tolbutamide, and trazodone. The disposition of cephradine, ibuprofen, and tolbutamide follows monoexponential decline, while trazodone exhibits biexponential characteristics. Cephradine represents a case where the C_{max} and T_{max} may be similar between the test and the reference formulations. In contrast, ibuprofen is an example where the C_{max}'s are similar between products, but the T_{max}'s differ between the formulations. Tolbutamide is a slow-absorbing drug relative to the other three formulations.

Bioequivalence Studies

Normal, healthy male volunteers, 18–50 years old, were recruited for the studies. Good health was confirmed by medical history, physical examination, and laboratory tests. Informed consent was obtained from each subject. All subjects were instructed to abstain from taking any medication or alcohol 1 week prior to and throughout the study.

The protocols for all studies were designed as two-treatment, two-period crossovers, with a washout interval of 1 week between the phases of the treatments.

Cephradine

Eighteen subjects completed this clinical trial. The drug treatments were cephradine and cephradine dihydrate capsules. After fasting for 8 hr, each subject received a 500-mg capsule of the respective cephradine formulation with 240 ml of water. Blood samples were drawn at 0, 20, 30, and 40 min and at 1, 1.5, 2, 3, 4, 5, 6, 8, and 10 hr after drug administration.

A microbiological assay (8) was used to analyze plasma samples of cephradine. All standards were prepared daily with dilutions made with buffer. Standard curves were linear over the concentration range 0.5–2.0 μg/ml. Any plasma samples with cephradine concentrations >2.0 μg/ml were appropriately diluted prior to being assayed. The assay sensitivity was 0.5 μg/ml.

Ibuprofen

The study was conducted as a two-way crossover, with 22 subjects comparing a test ibuprofen capsule with a reference ibuprofen tablet (Nuprin). The volunteers were fasted overnight until 4 hr after dosing (200-mg dose). Blood samples were drawn at 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hr postdose.

Serum concentrations of ibuprofen were determined by an HPLC method (9). Linearity was observed between 1 and 100 μg/ml, with a coefficient of variation of 10% at 7 μg/ml and 5% at 100 μg/ml. Assay sensitivity was 1 μg/ml.

Tolbutamide

Nineteen subjects completed this crossover study. Following a 10-hr fast, each subject received a single oral 500-mg dose of either the test (a generic tolbutamide tablet) or reference (Orinase Tablet) product with 6 oz of water. The subjects continued to fast for 4 hr following drug administration.

Blood samples (10 ml) were collected into evacuated collection tubes at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16, 24, 36, and 48 hr after dosing. Serum was separated by centrifugation and samples were immediately frozen at −15°C until assayed.

Tolbutamide levels in serum were measured by an HPLC method (10). The method was linear from 2.5 to 100 μg/ml. The sensitivity of the assay was 2.5 μg/ml. Day-to-day reproducibility of the assay yielded a coefficient of variation of 3.2% at a concentration of 14.91 μg/ml and 7.3% at 58.33 μg/ml. Accuracy of the assay averaged 97.2% at 60 μg/ml and 99.4% at 15 μg/ml. Recovery of the assay ranged from 97 to 103%.

Trazodone

A total of 27 subjects completed the study. Subjects fasted for 10 hr prior to drug administration. The test product was a generic version of the trazodone HCl tablet, and the reference product was a Desyrel Tablet. Each subject was given a single 100-mg dose (2 × 50-mg tablet) of either the test or the reference formulation. Subjects were not allowed to lie down for 12 hr after dosing. Blood samples (8 ml) were collected at 0, 20, 40, 60, 80, 100, and 120 min and 2.5, 3, 4, 5, 6, 8, 10, 12, 18, 24, 36, 48, and 72 hr after drug administration.

Trazodone levels in plasma were analyzed by an HPLC method (11). The assay was linear over the concentration ranges 0–500 and 500–4000 ng/ml. The within-day precision in terms of coefficient of variation was 1.2–4.5%, and the

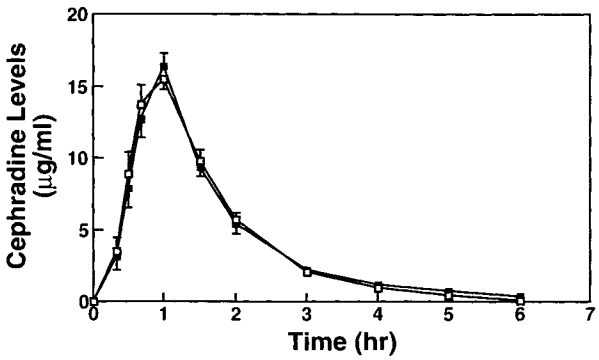

Fig. 1. Mean plasma concentrations of cephradine following a single 500-mg dose of a cephradine capsule (□) or a cephradine dihydrate capsule (□). Values represent the mean ± SE of 18 subjects.

Table I. Summary Statistics of Pharmacokinetic Parameters After an Oral 500-mg Dose of Cephradine[a]

Parameter	Mean ± SD		90% confidence interval
	Test	Reference	
AUC_{0-t}, μg · hr/ml	25.3 ± 3.1	24.7 ± 2.7	(99.9, 105.8)
AUC_{inf}, μg · hr/ml	25.7 ± 3.1	25.1 ± 2.7	(99.8, 105.7)
C_{max}, μg/ml	18.3 ± 0.6	17.4 ± 0.6	(96.6, 113.8)
T_{max}, hr	1.03 ± 0.06	0.83 ± 0.06	—
$AUC_{0-Tmax(i)}$, μg · hr/ml	8.1 ± 3.09	5.7 ± 1.88	(113.9, 170.6)
$AUC_{0-Tmax(R)}$, μg · hr/ml	5.97 ± 4.07	5.74 ± 1.88	(76.9, 131.5)
$AUC_{0-Tmax\dagger}$, μg · hr/ml	4.75 ± 2.86	4.81 ± 2.11	(71.1, 126.4)
$AUC_{0-0.67hr}$, μg · hr/ml	3.35 ± 2.05	3.54 ± 2.36	(63.1, 126.8)
AUC_{0-1hr}, μg · hr/ml	8.4 ± 2.93	8.4 ± 3.19	(81.0, 120.5)
$AUC_{0-1.5hr}$, μg · hr/ml	15.14 ± 3.03	14.68 ± 2.81	(92.6, 114.1)

[a] $T_{max(i)}$ = peak time for each formulation in each individual; $T_{max(R)}$ = peak time for reference formulation in each individual; $T_{max\dagger}$ = peak time of a formulation whichever occurs earlier in each individual. Confidence interval is expressed as the percentage of the reference mean.

between-day precision was 2.4–6.3%. Recovery of the assay ranged from 90 to 101%.

Data Analysis

Briefly, the "partial area method" involves calculation of partial area under the plasma/serum concentration–time curve (partial AUC) from time 0 to t, where t is the cutoff time around the T_{max} of the drug. Various cutoff points or times were tested for calculating the partial AUCs, including $T_{max(i)}$, $T_{max(R)}$, $T_{max\dagger}$, and some common time points before or after T_{max}, where

$T_{max(i)}$ = peak time for each formulation in each individual,

$T_{max(R)}$ = peak time for reference formulation in each individual, and

$T_{max\dagger}$ = peak time of a formulation, whichever occurs earlier in each individual.

The linear trapezoidal rule is used for calculation of partial AUCs. For comparison purposes, bioavailability parameters of AUC_{0-t}, AUC_{inf}, C_{max}, and T_{max} were also obtained for the studies. The AUC_{0-t}, where t represents the last measurable time point, was calculated using the linear trapezoidal rule and the AUC_{t-inf} was estimated by extrapolation as described previously (12). The AUC_{inf} was thus the sum of AUC_{0-t} and AUC_{t-inf}. The C_{max} and T_{max} were observed values following the administration of the drug.

Statistical Analysis

To facilitate bioequivalence evaluation, standard analysis of variance was performed on the partial AUCs using the SAS General Linear Model (GLM) procedure. The statistical model was partitioned into sequence, subject within sequence, period, treatment, and an error term. The two one-sided hypotheses at the $\alpha = 0.05$ level of significance were tested by constructing the 90% confidence intervals for the difference of the two means (test versus reference) (13).

RESULTS AND DISCUSSION

Cephradine

The mean plasma level-versus-time profiles of cephradine for the test and reference formulations are shown in Fig. 1. This is a case where the C_{max}, T_{max}, and true absorption rate may be similar between the test and reference formulations. Plasma levels of cephradine peaked at approximately 1 hr after administration of both test and reference formulations. The absorption process of the drug, based on the ap-

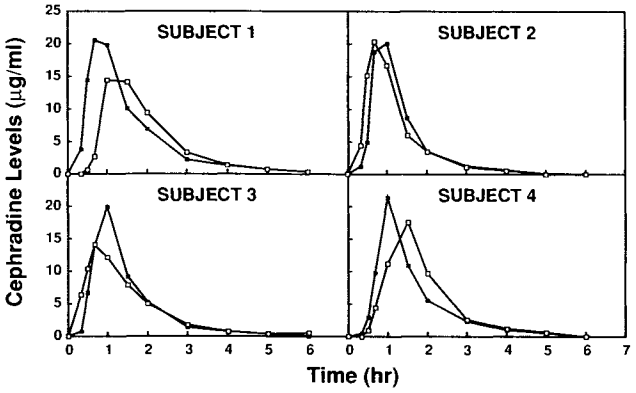

Fig. 2. The plasma concentration–time profile of cephradine in subjects 1–4 following a single 500-mg dose of a cephradine capsule (■) or a cephradine dihydrate capsule (□).

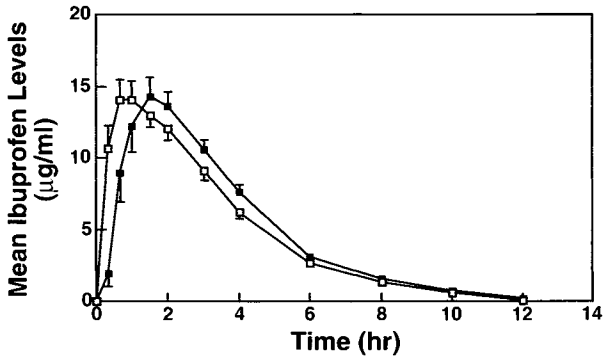

Fig. 3. Mean serum concentration of ibuprofen following a single 200-mg dose of an ibuprofen tablet (■) or a Nuprin capsule (□). Values represent the mean ± SE of 22 subjects.

Table II. Summary Statistics of Pharmacokinetic Parameters After an Oral 200-mg Dose of Ibuprofen[a]

Parameter	Mean ± SD		90% confidence interval
	Test	Reference	
AUC_{inf}, μg · hr/ml	60.3 ± 10.4	58.8 ± 10.2	—
C_{max}, μg/ml	19.6 ± 5.0	19.2 ± 3.3	(90.8, 113.1)
T_{max}, hr	1.59 ± 0.81	1.06 ± 0.8	—
$AUC_{0-Tmax(R)}$, μg · hr/ml	8.15 ± 11.7	9.70 ± 5.55	(56.7, 117.7)
$AUC_{0-Tmax\dagger}$, μg · hr/ml	4.17 ± 4.19	7.09 ± 4.70	(34.1, 87.6)
AUC_{0-1hr}, μg · hr/ml	5.68 ± 5.32	10.65 ± 5.0	(24.8, 85.0)
AUC_{0-2hr}, μg · hr/ml	19.28 ± 8.97	23.68 ± 7.16	(61.4, 102.9)

[a] $T_{max(R)}$ = peak time for reference formulation in each individual; $T_{max\dagger}$ = peak time of a formulation, whichever occurs earlier in each individual. Confidence interval is expressed as the percentage of the reference mean.

proximation of the Wagner–Nelson method (12), is essentially complete at 1 hr after dosing.

Table I presents summary statistics for the pharmacokinetic parameters that may be employed in the evaluation of absorption rate. The mean differences in C_{max} and T_{max} values are relatively small between the two formulations and the 90% confidence interval (CI) of C_{max} falls well within the ±20% range. The CI of T_{max} was not calculated in view of the fact that this parameter is used mainly as a qualitative check on the rate of absorption but is rarely pivotal in a bioequivalence determination (14).

The mean absorption rates of cephradine for both formulations may be similar, as depicted by the superposition of the rising phase for both plasma profiles (Fig. 1). Nevertheless, on an individual basis, as shown by the examples of subjects 1–4 (Fig. 2), there is a fairly high variability in the input rate between the two formulations tested. This is reflected by the large standard deviations and wide window of CIs calculated for partial AUCs (Table I).

From a bioequivalence point of view, the peak time of the reference formulation appears to be a desirable cutoff point for partial AUC calculation. In the case of cephradine, using the current statistical criteria for bioequivalence, while equivalency in absorption rate may be claimed based on the C_{max} parameter, the two formulations would be declared bio*in*equivalent based on $AUC_{0-Tmax(R)}$. This is attributable to the high sensitivity of $AUC_{0-Tmax(R)}$ to the formulation difference in the absorption rate of the drug.

Clearly, the determinations of equivalency in rate of absorption rely highly on the cutoff time point (t_{cutoff}) chosen for calculation, unless the formulations tested have similar rates of absorption throughout the entire absorption phase. As in the case of cephradine, with the exception of $AUC_{0-1.5\ hr}$, the 90% CI is outside the ±20% limit for each partial AUC parameter calculated. In general, when $t_{cutoff} > T_{max}$, the farther the cutoff time from the peak time, the tighter the confidence interval becomes.

The use of $AUC_{0-Tmax(i)}$ in the evaluation of absorption rate is handicapped, however, by the fact that identical $AUC_{0-Tmax(i)}$ values may be obtained for two formulations that have distinctly different rates of absorption of the drug; i.e., the plasma concentration–time profile for the test product has a steeper rising absorption phase with a shorter T_{max} and a higher C_{max} than that for the reference product. In this regard, it can be envisaged that in order to make a fair comparison, the cutoff point for partial AUC calculation should be at least some time common to both formulations in each individual. Therefore, $AUC_{0-Tmax(i)}$ has little utility as a parameter for assessment of absorption rate in bioequivalence evaluations.

Ibuprofen

Figure 3 presents the mean serum profiles for ibuprofen after the administration of the test and reference products. The summary statistics are given in Table II.

This is a case where the C_{max} or T_{max} values may be similar between the test and the reference formulations, but the rates of absorption are clearly different for the two products. As noted, the reference product is absorbed much faster than the test product. However, the 90% CI of C_{max} falls within the acceptable ±20% range. In contrast, this difference in the absorption rates is readily shown by the use of partial AUCs. The intervals calculated for all the partial AUCs (up to 2 hr) unequivocally fall outside the acceptable range, with the lower end well below the 80% limit.

Tolbutamide

Figure 4 shows the mean serum level–time profiles for tolbutamide after administration of the test and reference formulations. Table III outlines the summary statistics for both formulations.

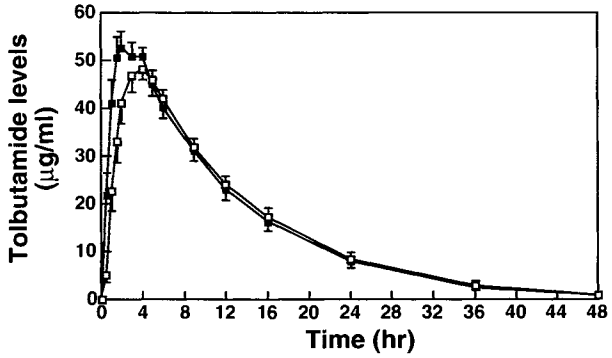

Fig. 4. Mean serum concentrations of tolbutamide following a single 500-mg dose of a generic tolbutamide tablet (■) or an Orinase Tablet (□). Values represent the mean ± SE of 19 subjects.

Table III. Summary Statistics of Pharmacokinetic Parameters After an Oral 500-mg Dose of Tolbutamide[a]

Parameter	Mean ± SD		90% confidence interval
	Test	Reference	
AUC_{0-48hr}, μg · hr/ml	710.1 ± 263	694.7 ± 257	—
AUC_{inf}, μg · hr/ml	730.9 ± 314	712.6 ± 306	—
C_{max}, μg/ml	62.2 ± 9.95	55.33 ± 9.41	(105.6, 119.1)
T_{max}, hr	2.16 ± 1.17	3.21 ± 1.32	—
$AUC_{0-T max(R)}$, μg · hr/ml	128.9 ± 67.2	85.4 ± 24.8	(124.6, 175.9)
$AUC_{0-T max†}$, μg · hr/ml	60.9 ± 32.5	36.7 ± 30.4	(121.2, 206.7)
AUC_{0-1hr}, μg · hr/ml	21.2 ± 15.1	8.2 ± 7.0	(166.0, 347.4)
$AUC_{0-1.5hr}$, μg · hr/ml	44.2 ± 23.6	22.1 ± 16.2	(140.3, 255.9)
AUC_{0-2hr}, μg · hr/ml	70.0 ± 30.0	40.7 ± 25.4	(129.2, 212.6)
AUC_{0-3hr}, μg · hr/ml	121.8 ± 40.4	84.6 ± 39.6	(116.2, 169.1)
AUC_{0-4hr}, μg · hr/ml	172.6 ± 45.8	132.2 ± 48.1	(111.5, 147.7)

[a] $T_{max(R)}$ = peak time for reference formulation in each individual; $T_{max†}$ = peak time of a formulation, whichever occurs earlier in each individual. Confidence interval is expressed as the percentage of the reference mean.

This is a case where the drug is slowly absorbed and peak time is delayed until hours after dosing. As indicated in Table III, the 90% CI for C_{max} is within the 20% limit. However, there is an appreciable difference in T_{max} (approximately 1 hr) between the two formulations. As with the case of ibuprofen, the difference in the input rate is manifested by the CIs computed for partial AUCs (up to 4 hr after dosing). Note that the absorption process of tolbutamide, approximated by the Wagner–Nelson method, is almost complete at 4 hr (range, 1.5–4 hr) after drug administration.

Trazodone

The mean plasma level–time profiles of trazodone are shown in Fig. 5. The corresponding summary statistics for trazodone are listed in Table IV.

Trazodone represents a case of a fast-absorbing drug which is similar to cephradine. The average T_{max} for the drug is about 1 hr. When the $t_{cutoff} \geq 1.5$ hr, the CIs for partial AUCs fall within the ±20% range for each parameter. Based on the lower limit of the CI, the test formulation of trazodone would be unacceptable for $AUC_{0-T max†}$ but acceptable for $AUC_{0-T max(R)}$. The disparity in the outcome is due to the fact that $AUC_{0-T max†}$ involves truncation of area at an earlier time than $AUC_{0-T max(R)}$ in some cases.

CONCLUSION

As exemplified by the present data, the cutoff point for partial AUCs should be a common time for both test and reference products in each individual so that a fair comparison of absorption rates can be made. It is pertinent to define the time interval over which the average rate of absorption is assessed if the proposed method is to be used for bioequivalence evaluations.

Strictly, a rigorous bioequivalency comparison between absorption rates of a drug for two formulations can be made only when the cutoff point falls at the T_{max} of the reference formulation or at some time no later than the earlier T_{max} produced by whichever formulation tested. The applicability of $AUC_{0-T max(R)}$ in a bioequivalence setting may not be fully assessable in this study because of the limited data presented. Nevertheless, it is predictable that in most cases, $AUC_{0-T max†}$ would fail to meet the present 80–120% criterion. Only when the cutoff point approaches some time t (may range from 0.5 to 1 hr) after the peak time (T_{max}) will the partial AUC_{0-t} yield comparable results with C_{max}. Conceivably, if $AUC_{0-T max†}$ (or possibly $AUC_{0-T max(R)}$) is the parameter of choice for the "partial area method," the statistical or decisional criteria of ±20% may have to be relaxed.

It was suggested (15) that the $AUC_{0-T max(R)}$ ratios are not reliable indicators of the absorption rate, as they failed to indicate equivalence in instances when the absorption rate constant (K_a) and relative bioavailability (F) were within the acceptable 20% of the reference value; and further, they failed to indicate *in*equivalence for a product with a high F and a low K_a compared to the reference formulation. The reason for the former observation is that the $AUC_{0-T max(R)}$ ratio is such a sensitive parameter that a slight difference in the absorption rate of the drug can be detected, as has been shown by the examples described in this paper. The explanation for the latter finding, however, stems from a fundamental concept. The absorption rate constant (such as K_a) alone cannot be used for rate comparisons because this parameter is scale independent; it considers only the shape and

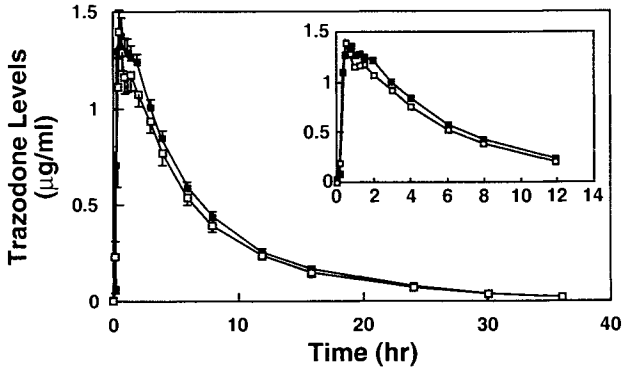

Fig. 5. Mean plasma concentrations of trazodone following a single 100-mg dose of a generic trazodone HCl tablet (■) or a Desyrel Tablet (□). Values represent the mean ± 27 subjects.

Table IV. Summary Statistics of Pharmacokinetic Parameters After an Oral 100-mg Dose of Trazodone[a]

Parameter	Mean ± SD		90% confidence interval
	Test	Reference	
AUC_{0-t}, μg · hr/ml	10.6 ± 2.4	9.5 ± 3.6	(95.5, 112.1)
AUC_{inf}, μg · hr/ml	11.1 ± 2.9	10.8 ± 3.4	(97.1, 116.8)
C_{max}, μg/ml	1.68 ± 0.4	1.64 ± 0.51	(91.1, 114.9)
T_{max}, hr	1.09 ± 0.75	1.14 ± 1.0	—
$AUC_{0-Tmax(R)}$, μg · hr/ml	1.04 ± 1.21	0.98 ± 0.91	(85.8, 108.4)
$AUC_{0-Tmax\dagger}$, μg · hr/ml	0.55 ± 0.64	0.63 ± 0.58	(71.9, 101.2)
$AUC_{0-1.5hr}$, μg · hr/ml	1.53 ± 0.45	1.61 ± 0.46	(82.9, 104.5)
AUC_{0-2hr}, μg · hr/ml	2.18 ± 0.59	2.19 ± 0.53	(89.4, 108.4)
AUC_{0-3hr}, μg · hr/ml	3.25 ± 0.62	3.22 ± 0.66	(93.1, 107.8)

[a] $T_{max(R)}$ = peak time for reference formulation in each individual; $T_{max\dagger}$ = peak time of a formulation, whichever occurs earlier in each individual. Confidence interval is expressed as the percentage of the reference mean.

not the magnitude, of the drug level curve. In contrast, as indicated by $AUC_{0-Tmax(R)}$, similar rates of absorption (in terms of amount/time) over a time interval (e.g., in this case, from time 0 to the peak time of the reference product) may be found between the two formulations.

It appears that the choice of cutoff point for bioequivalence comparisons would depend on both the peak time of the drug level curve and the therapeutic use of the drug under study. For instance, ibuprofen is an antiinflammatory drug indicated for temporary relief of pain. The rate of absorption of ibuprofen is critical to its pharmacological action, and thus an initial rate of absorption would be a major concern for the drug. In this case, the employment of $AUC_{0-Tmax\dagger}$ or $AUC_{0-Tmax(R)}$ may be preferred for evaluation. On the other hand, for trazodone, which acts as an antidepressant, an average absorption rate would be the subject of interest, and therefore, the cutoff point may be extended to some time beyond T_{max}.

Overall, the preliminary results of the present study indicate that the "partial area method" may serve as an alternative technique for the assessment of relative absorption rates in bioequivalence studies. Questions may be raised as to whether the method will reflect the magnitude of the true difference in absorption rate between formulations or the method will fail to indicate equivalency in absorption rate when, in fact, the test and reference formulations are bioequivalent. To address these concerns, both simulations and comparisons to the real data collected from bioequivalence studies are warranted. Further investigation of the ultimate utility of the method in bioequivalence evaluation is currently under way in the Agency.

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