Metrics Comparing Simulated Early Concentration Profiles for the Determination of Bioequivalence

Laszlo Endrenyi,[1,3] Ferenc Csizmadia,[1] Laszlo Tothfalusi,[1] and Mei-Ling Chen[2]

Received February 9, 1998; accepted April 20, 1998

Purpose. To compare the effectiveness of various metrics which evaluate bioequivalence in the early phase of concentration-time profiles.
Methods. Two-period crossover trials were simulated with increasing assumed ratios of the true absorption rate constants of the two formulations, and with various kinetic models. Kinetic sensitivities (KS) and standard errors (SE) of the various metrics were recorded and the percentage of trials accepting bioequivalence (the statistical power) was evaluated. The principal metrics included the partial AUC (AUC_p), the intercept obtained by linear extrapolation of the ratios of the lower over higher concentrations (C) measured for the two formulations ($I_{L/H}$), and the ratios of intercepts extrapolated from logarithmic C/t time values of the two products (M_{log}). For comparison, also properties of C_{max} and an ideally evaluated measure (Id) were determined.
Results. M_{log} showed generally the highest statistical power and KS, and also the largest SE, closely followed by $I_{L/H}$. Partial AUC exhibited lower power and KS, but also smaller SE than the intercept procedures. The three methods had much higher power, KS and SE than C_{max}. These comparisons were maintained over various kinetic conditions and experimental designs. The effective evaluation of bioequivalence in the early phase of studies is assured witb 3 (or more) measurements until the population average peak of the reference formulation.
Conclusions. The three principal methods assess bioequivalence very effectively in the early phase of a concentration-time profile. M_{log} had the highest statistical power, closely followed by $I_{L/H}$ and then by partial AUC.

KEY WORDS: bioequivalence; intercept metric; early exposure; absorption rate; partial AUC; experimental design.

INTRODUCTION

The determination of bioequivalence assessing the similarity of plasma concentration (C)-time (t) profiles of two drug formulations in their early phases has been of interest in recent years. Chen (1) proposed that the area under the curve (AUC) contrasting concentrations with time should be determined for an early, limited duration. This partial AUC (AUC_p) should be a useful measure for the assessment of bioequivalence. Endrenyi and Al-Shaikh (2) suggested that ratios of early concentration measurements (C_T/C_R), or their logarithms, of the test (T) and reference (R) drug products should be formed. The ratios, or their logarithms, should be extrapolated by linear regression to the time of zero. The calculated intercept is a measure of the ratio of initial absorption rates, or its logarithm, of the two formulations. Macheras et al. (3) modified the intercept procedure by extrapolating to the time of zero, separately for both formulations, early recordings in the plot of either (C/t) *vs.* t or log(C/t) *vs.* t. The ratio of the two intercepts is a measure of the ratio of initial absorption rates.

Traditionally, the maximum concentrations (C_{max}) of the two formulations have been used to evaluate comparative absorption rates and, more generally, the contrasting behaviours of concentration-time profiles in their early phase. However, calculations and simulations demonstrated that C_{max} has in fact poor kinetic and statistical properties (4–8).

Tozer et al. (9) recently suggested that the bioequivalence of two drug formulations could be assessed by determining the similarity of three metrics: AUC, C_{max} as a measure of drug safety, or peak exposure, and an index comparing the concentration-time profiles in their early phase more effectively than C_{max}.

Therefore, the present study will evaluate and compare the effectiveness of various procedures which could be used for the determination of bioequivalence in the early phase of the concentration-time profiles. The methods will include the partial AUC, intercept and modified intercept procedures as well as some of their improvements. Performances of C_{max} and of an ideal analysis will be included for comparison.

METHODS

Kinetic and Statistical Models

A kinetic model assuming first-order drug absorption and disposition, with a single exponential term, was used in most simulations ('basic scenario'). The parameters and their inter- and intraindividual variations, summarized in Table I, were generally identical to those given by Bois et al. (5). As a deviation from the conditions of Bois et al. (5), the parameters V (apparent volume of distribution), CL (clearance) and k_a (absorption rate constant) were assumed to have lognormal instead of truncated normal distributions. The assumed population average absorption rate constant of the test formulation was varied in comparison with that of the reference formulation.

Experimental Design

The basic design contained observations at times of 0, .15, .30, .45, .6, .8, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 3.5, 4, 5, 6 and 8 hours. These sampling points placed greater emphasis on measurements in the early stage of an investigation than the design applied by Bois et al. (5). Another condition used the presence of only half of the observations by omitting every second timing, i.e., measurements were set at 0, .30, .6, 1.0, 1.5, 2, 3, 4 and 6 hours.

This is illustrated in Figure 1 in which the large dots indicate the timings of the sparse design while all points are included for the full sampling scheme. In addition to the reference curve, the diagram includes concentration profiles for the test formulation with k_{aT} values corresponding to the given bioequivalence limits (see below) at $k_{aT}^{\circ}/k_{aR}^{\circ} = 0.501$ and 2.767. (The superscript $^{\circ}$ indicates true conditions before the superimposition of parameter and concentration variations.) The illustrated curves represent population averages around which the responses fluctuate.

[1] Department of Pharmacology, University of Toronto, Toronto, Ontario M5S 1A8, Canada.
[2] Food and Drug Administration, Center for Drug Evaluation and Research, Rockville, Maryland.
[3] To whom correspondence should be addressed. (e-mail: l.endrenyi@utoronto.ca)

0724-8741/98/0800-1292$15.00/0

Table I. Distributions, Means, Coefficients of Variation (CV) of Simulated Parameters

Parameter	Distribution	Mean (1-comp't)	Mean (2-comp't)	CV[a] (%)
Volume of distribution, V (L kg^{-1})	Lognormal	1	1	10
Clearance, CL (L hr^{-1} kg^{-1})	Lognormal	0.347	0.5	20
Absorption rate constant, k_a (hr^{-1})	Lognormal	1.39	2	20
Central to peripheral rate constant, k_{12} (hr^{-1})	Lognormal	-	0.2 (Model I)	20
			1.25 (Model II)	20
Peripheral to central rate constant, k_{21} (hr^{-1})	Lognormal	-	0.05 (Model I)	20
			0.3125 (Model II)	20
Bioavailability, F	Uniform	0.5	0.5	(11.5)[b]

[a] Coefficient of variation for both inter- and intrasubject variabilities.
[b] Uniform distribution with a range of 0.4–0.6 for intersubject variation, corresponding to CV = 11.5%, and a range of −0.1 to 0.1 for intraindividual variabilities.

Simulated Bioequivalence Trials

For the simulation of observations, normally distributed concentrations were assumed which had means equaling the responses predicted by the kinetic model in each subject and with both formulations. Following Bois et al. (5), the variance model had two components. A constant term equalled 0.1LQ where LQ, the limit of quantitation, was assumed to be $0.01C^{\circ}_{max}$. The second term had a coefficient of variation equaling 10% of the true concentration. In order to obtain the conditions of a two-period crossover trial, 24 subjects were assumed to be assigned randomly to two sequences of drug administration. 1,000 trials were simulated under each condition. Various metrics were obtained from the concentration profiles recorded during both periods in each subject. The average and, based on the usual ANOVA, the standard error (S.E.) of the individual logarithmic ratios were calculated in each trial. The acceptance or rejection of bioequivalence (see below: "power curves") was also recorded in each trial.

Estimated Metrics

Properties of numerous metrics and methods of analysis were explored. Only those being most favourable or relevant or showing the best promise have been retained in this presentation.

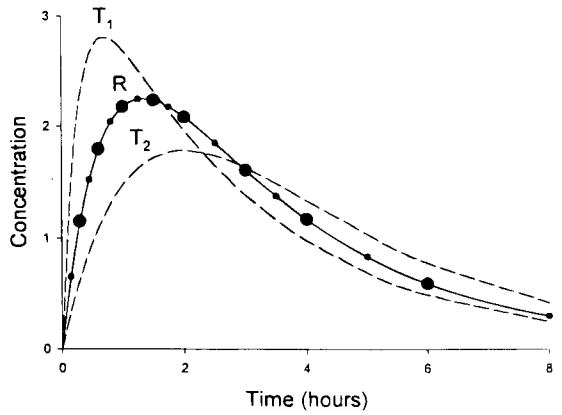

Fig. 1. Experimental design applied in the simulations. The large dots on the reference (R) curve show the sampling points with the sparse design. All points are included in the full design. The two curves illustrating the concentration profile of the test formulation (T_1 and T_2) are displayed at the bioequivalence limits of the ratios of absorption rate constants ($k^{\circ}_{aT}/k^{\circ}_{aR}$ = 0.501 and 2.767).

Partial AUC (AUC_p)

AUCs were evaluated by the trapezoidal rule from the start of an investigation (i.e., from a time of zero, t = 0) until the time of the earlier peak (the peak with the smaller observed time to maximum, T_{max}) since this range of timings was found to yield the statistically most powerful results (10).

Intercept Metric (I)

Three procedures applying the intercept approach were initially evaluated. The first, linear method (*I*) extrapolated the concentration ratios (C_T/C_R) of the test and reference formulations which were recorded in the early phase of a study (2). According to the second approach, the logarithms of concentration ratios (log (C_T/C_R)) were extrapolated (I_{log}) and the antilog of the intercept was calculated (2). The third approach was new. The formulations were identified according to whether the measured concentration was the higher or lower reading at the time preceding the earlier peak. The assignment of formulations to the "lower" and "higher" concentrations was then maintained at each earlier time point. The ratio of concentrations (C_{Lower}/C_{Higher}) was formed at these times, and the intercept was obtained from them by linear regression ($I_L/_H$).

Modified Intercept Metric (M)

Two principal procedures were analyzed which paralleled the first two approaches described for the intercept metric. The first method calculated C/t values, again in the early stage of an investigation. Intercepts were obtained by linear regressions calculated against time, separately for the two formulations, and ratios of the intercepts were evaluated (3) (*M*). The second procedure calculated the intercepts from log(C/t) values (3) (M_{log}).

Maximum Concentration (C_{max})

C_{max} was evaluated for comparisons with the other methods. The metric was obtained in the usual way by recording the largest observed plasma concentration.

Ideal Measure (Id)

The performances of metrics were compared with that of an ideal measure (*Id*) representing a limiting case. The intercept metric and its modifications estimate ratios of $k_a \cdot F \cdot Dose/V$ where F is the fraction of dose reaching the systemic circulation and V the apparent volume of distribution. The effectiveness of this quantity is illustrated by assuming variations only in the parameters but not in the observations.

Methods of Evaluation

Power Curves

The effectiveness of a metric assessing bioequivalence is ultimately indicated by the characteristics of power curves. They present the probability (in practice, the percentage of simulated crossover trials) of accepting the statement of bioequivalence when an underlying measure (here the k^o_{aT}/k^o_{aR} ratio) is varied. In the absence of concentration and parameter variations, all studies should signal the acceptance of bioequivalence when the underlying measure is within its preset limits, and all investigations should reject bioequivalence when the measure is outside its limits. Thus, a square pattern is obtained when the proportion of accepted bioequivalence trials is plotted against the k^o_{aT}/k^o_{aR} ratio. In the presence of concentration and parameter variations, the course of accepting and rejecting bioequivalence deviates from this square pattern. In a comparison of two metrics, the one exhibiting smaller deviations from the square pattern (i.e., the one having smaller statistical responsiveness (8)) should be favoured. Correspondingly, at a given ratio of k^o_{aT}/k^o_{aR}, the metric declaring the higher proportion for the acceptance of bioequivalence should be preferred. This characterization assures that, at a given consumer risk, usually 5% (observed at the bioequivalence limits), the producer risk (recorded at the condition of bioequivalence) is maximized.

In order to enable the comparison of metrics, their bioequivalence limits should be the same, i.e. they should exhibit a coincident square pattern under the ideal condition. These limits were assumed to correspond to a range of 0.80–1.25 for the ratio of $C^o_{max,T}/C^o_{max,R}$. The corresponding limits of the k^o_{aT}/k^o_{aR} ratio were calculated from the kinetic models in the basic scenario, under the chosen condition, to be 0.501 and 2.767. The bioequivalence limits of each metric were determined from its kinetic sensitivities (see below). Consequently, calculation of the limits, i.e. the adjustment of the "goalposts," was different for each metric as Rostami-Hodjegan et al. (6) suggested and Endrenyi et al. (11) applied.

Kinetic Sensitivity

Kinetic sensitivity expresses the relationship between a metric and an underlying measure, the absorption rate constant in the present case. Two procedures were applied for its evaluation. The first compared ratios of metrics with ratios of k^o_a at selected values of the latter. In the second approach, the relationship between the logarithm of ratios of a metric and logarithmic ratios of k^o_a was depicted. The slope of this plot is closely related to kinetic sensitivity, a slope of 1.0 in absolute magnitude indicates full kinetic sensitivity. Kinetic sensitivities were obtained from simulated crossover trials. This was required for procedures related to the intercept method. The sensitivities of these methods depended somewhat on the experimental design. In contrast, kinetic sensitivities of C_{max}, C_p and *Id* could be calculated without simulations and did not depend on the experimental design.

Standard Error

Standard errors (S.E.) comparing the logarithmic averages of the metrics of the formulations were calculated from the residual mean square errors of ANOVAs in each trial. These were used for the assessment of 90% confidence intervals of the logarithmic metrics and the determination of bioequivalence by the two one-sided tests procedure (12). Square roots of means of the squared values are presented.

Additional Kinetic Conditions

Paralleling the studies of Bois et al. (5) and Tothfalusi and Endrenyi (13), the performances of the three principal investigated metrics were evaluated under additional kinetic conditions ('scenarios'). They included the conditions of low absorption/elimination rates ('flip-flop' kinetics), zero-order absorption, and two two-compartmental distribution kinetic models.

In the condition of low absorption/elimination ratio, the true absorption rate constant of the reference formulation was set at $k^o_{aR} = 0.0867 hr^{-1}$, and consequently $k^o_{aR}/k^o_{aT} = 0.25$ instead of 4.0 as in the basic scenario.

For the study of zero-order absorption kinetics, the duration of infusion (input) time was fixed at $2/k^o_{aR} = 1.44$ hr thereby maintaining identical mean absorption times between zero- and first-order inputs. By varying k^o_{aT}, the infusion time of the test preparation was made to be shorter or longer than that of the reference formulation. The intra- and interindividual coefficients of variation for the lognormally distributed durations of infusion were 20%.

Both two-compartmental models assumed first-order absorption, distribution and elimination. In both models, the ratio k^o_{12}/k^o_{21} (central to peripheral over peripheral to central distribution rate constants) was set at 4, the absorption rate constant $k^o_a = 2.0\ hr^{-1}$ and the elimination rate constant $k^o_{10} = CL^o/V^o = 0.5\ hr^{-1}$ (Table I). In Model I, the ratio of elimination and distribution constants was $k^o_{10}/k^o_{21} = 2.5$ whereas in Model II, the ratio was $k^o_{10}/k^o_{21} = 0.4$. The properties of the parameters are summarized in Table I.

Number of Observations

The number of measurements required for the determination of bioequivalence by the various procedures was investigated. In this part of the study, the timings of the observations were equally spaced. The distance between timings was T^o_{max}/N where the number (N) of measurements between zero and T^o_{max} was fixed at 1, 1.5, 2, 3, 4, 5 or 6, and T^o_{max} was the time at the theoretical maximum concentration.

RESULTS

Screening of Investigated Methods

k^o_{aT}/k^o_{aR} values of 0.60 and 2.25 were chosen for the illustrative comparison of the various methods. These values were

perceived, from preliminary studies, to yield the greatest discrimination among acceptance rates for the bioequivalence of the procedures (see also Figs. 2 and 4). Tables II and III present the results obtained with the full and sparse sampling designs, respectively.

The various intercept procedures performed satisfactorily and only small differences were noted in their effectiveness. Still, the procedures utilizing ratios of lower/higher concentrations ($I_{L/H}$) and log(C/t) value (M_{log}) were, on the whole, the most favourable. In particular, they yielded high rates of acceptance for bioequivalence and high kinetic sensitivities. The logarithmic intercept method (I_{log}) was also attractive under some circumstances. Partial AUC showed generally lower standard errors but also somewhat lower power and kinetic sensitivity than $I_{L/H}$ and M_{log}. As expected, C_{max} had inferior properties for the determination of bioequivalence.

Based on the screening of the various procedures, three methods were selected for more detailed exploration. They included the partial AUC (AUC_p), the intercept approach utilizing ratios of the lower/higher concentrations ($I_{L/H}$), and the modified intercept method using log(C/t) (M_{log}). For comparison, results for C_{max} and for the limiting, ideal condition (Id) were also included.

Detailed Evaluation of the Principal Methods

Figures 2 and 4 present power curves of the 5 metrics with the full and sparse sampling schemes, respectively. The lower halves of the diagrams expand the extreme regions of the power curves in order to enable visual discrimination among the various methods. Figures 3 and 5 show the patterns of kinetic sensitivities and standard errors again with the full and sparse experimental designs, respectively. The diagrams amplify the conclusions reached in the screening.

There were only fairly small differences among the performances and characteristics of the 3 favoured methods. Their effectiveness, in comparison with the ideally achievable level, was quite satisfactory. Altogether, the modified intercept method (M_{log}) appeared to be the best for the assessment of bioequivalence, especially with fewer design points. The statistical powers and kinetic sensitivities of the two intercept metrics were very high, that of partial AUC somewhat lower. Partial AUC had the smallest standard error followed by the modified intercept metric.

The performances of the three metrics were strongly superior to that of C_{max}. However, the properties of C_{max} did not

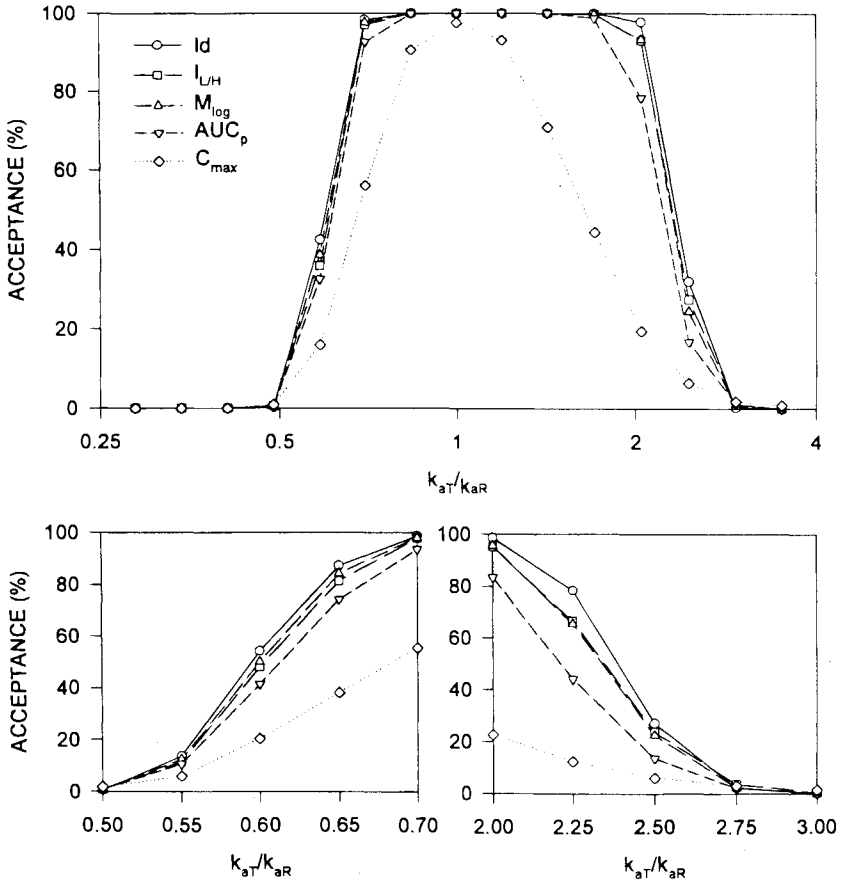

Fig. 2. Power curves showing the percentage of simulated crossover trials in which bioequivalence was accepted by applying various metrics. 1,000 trials were evaluated under each condition as the ratio of the absorption rate constants of the two formulations was gradually increased. Concentrations were assumed to be measured at 18 time points. The top panel presents the complete power curves whereas the lower panels magnify the regions which show sensitively the contrasts among the performances of the metrics.

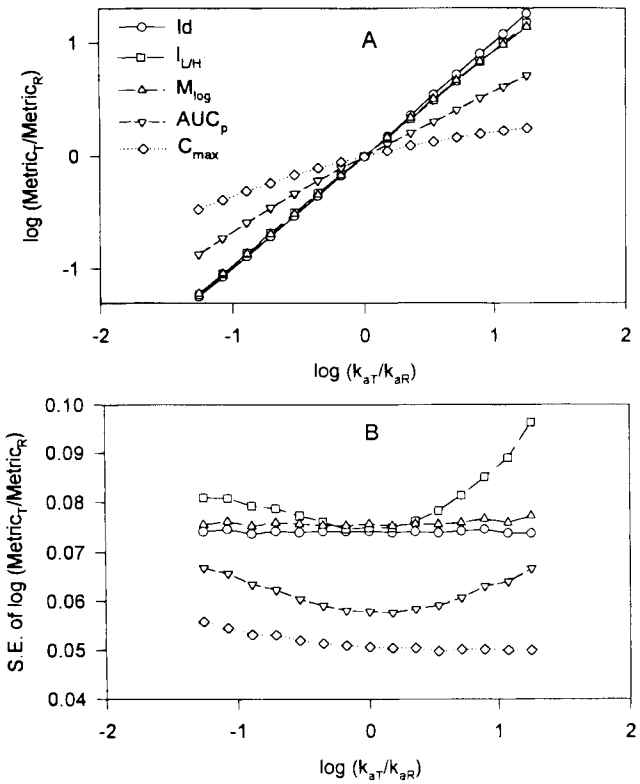

Fig. 3. (A) Kinetic sensitivities and (B) standard errors of ratios of metrics comparing test and reference formulations with the full design of 18 observations. Kinetic sensitivites are the slopes of the plots contrasting the logarithm of the metric ratio with $\log(k^0_{aT}/k^0_{aR})$. A slope of 1.0 represents full kinetic sensitivity. Standard errors were obtained from the ANOVAs of the simulated trials.

change with experimental design whereas those of the metrics were much affected (compare Tables II and III).

Additional Kinetic Conditions

Table IV presents the percentage of simulated crossover trials in which bioequivalence was accepted (i.e., the statistical power) for four additional kinetic conditions (see Table I). The results are summarized within the ascending segments of the power curves. Table IV includes the lower and upper bioequivalence limits under each condition as well as the k^0_{aT}/k^0_{aR} ratios at which the statistical powers are compared.

With zero-order absorption, the three principal metrics had very high efficiencies, very close to that attainable ideally (Table IV). The efficiencies were high also under the other investigated kinetic conditions, the flip-flop model and the two versions of two-compartmental models (Table IV).

In comparisons of the performances of the principal metrics, M_{log} and $I_{L/H}$ had similar statistical powers with M_{log} having slight advantage. The efficiency of AUC_p was generally trailing somewhat those of the other two metrics especially when $k_{aT}>k_{aR}$ (Table IV).

The power of C_{max} was low under all conditions.

Effect of Number of Observations

Figure 6 presents the percentage of simulated trials in which bioequivalence was accepted by the various methods when the number of observations until the population average reference peak (T^0_{max}) was gradually raised. The analysis was performed at two selected ratios of absorption rate constants, $k^0_{aT}/k^0_{aR} = 0.60$ and 2.25. These ratios were around the middle of the ascending segments of the power curves and thus enabled good discrimination (Figs. 2 and 4).

When the test formulation is absorbed more slowly than the reference product ($k^0_{aT}/k^0_{aR} = 0.60$), little improvement is seen in the effectiveness of the tests by raising the number of observations, recorded until the average reference peak time, beyond 3, or even 2 or 1 (Fig. 6A). Just a very few observations on the reference concentration profile assure in this case substantial information on the profile of the test formulation to enable the effective comparison of the two concentration-time curves.

The data requirements are higher when the absorption of the test product is faster than that of the reference formulation ($k^0_{aT}/k^0_{aR} = 2.25$). The power of the test is reduced substantially unless, on the average, 3 observations are obtained until the reference peak (Fig. 6B). 4 measurements to the true reference peak yield some improvement but additional observations result in only a small increase of power.

Altogether, the bioequivalence of drug formulations in the early phase of concentration-time profiles can be evaluated effectively by the investigated procedures if, on the average, 3 (or more) measurements are made until the population average peak time of the reference product.

DISCUSSION

The results indicate that early concentration profiles can be compared and bioequivalence evaluated effectively by the investigated procedures. In an initial screening, three methods were found to be particularly promising. They included the partial AUC measured until the earlier peak (AUC_p), the intercept obtained by the linear extrapolation of ratios of lower over higher of the concentrations measured for the two drug products in the early phase ($I_{L/H}$), and the ratio of the intercepts obtained from logarithmic C/t values of the two formulations (M_{log}).

In comparison with the ideally achievable power, the three principal methods evaluate bioequivalence very effectively in the early phase of an investigation. The two intercept metrics had similar performances. They showed high statistical power and kinetic sensitivity. Considering all conditions, the modified intercept method (M_{log}) extrapolating log(C/t) values was the most effective.

The statistical powers of analysis by partial AUC and by the intercept procedures were similar when only few observations were available until T^0_{max} and the test formulation was absorbed more slowly than the reference product. Under other conditions, the power shown by partial AUC was somewhat lower than the values observed with the intercept methods. Partial AUC had lower kinetic sensitivity but also smaller standard error than the intercept procedures.

The satisfactory performance of the three principal procedures was observed under various kinetic conditions. They included zero-order kinetics, two-compartmental disposition kinetics with two contrasting assumptions about the ratio of distribution rate constants to and from the peripheral compartment, and flip-flop kinetics (small ratio of absorption to elimination rates).

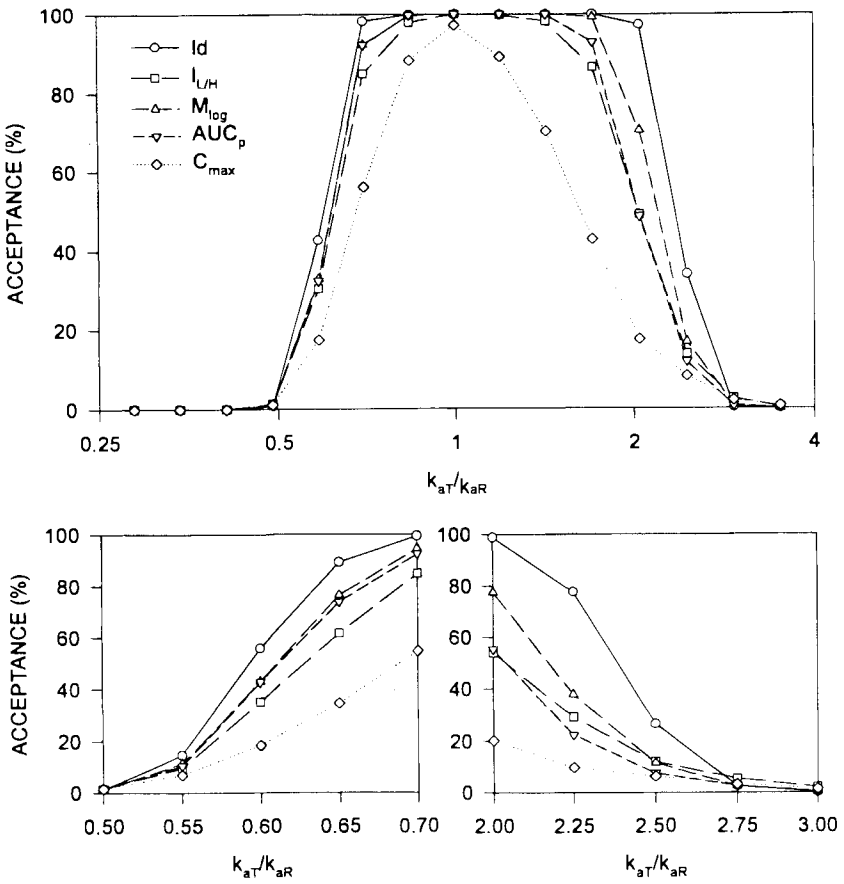

Fig. 4. Power curves for five metrics when the assumed design of the simulated crossover trials contained only 9 concentrations (see Fig. 1). The interpretation of the diagram is identical to that of Fig. 2.

The results of both the screening and detailed studies indicate that contrasts of kinetic sensitivity contribute to the comparisons of power curves to a larger extent than deviations between variations (standard errors). Notably, C_{max} shows small variation but also low kinetic sensitivity; the overall power of tests performed with this metric is very low.

When the evaluation of bioequivalence in the early phase of an investigation is of interest, i.e. when it is important that formulations should have comparable absorption rates, a larger than usual number of observations should be allocated to this segment. It is gratifying that the additional data requirement is moderate. An average of 3 measurements until the population average peak time of the reference formulation ($T^0_{max,R}$) is sufficient for the determination of bioequivalence with reasonably high power. 4 observations to the reference peak improve somewhat the effectiveness of the tests but additional measurements

Table II. Screening of Metrics with Full Design Scheme

	$k^o_{aT}/k^o_{aR} = 0.60$			$k^o_{aT}/k^o_{aR} = 2.25$		
Metric	Acc(%)	K.S.	S.E.	Acc(%)	K.S.	S.E.
Id	53.9	1.002	0.074	76.9	0.996	0.074
C_{max}	19.5	0.707	0.052	12.8	0.532	0.050
AUC_p[a]	42.3	0.826	0.061	44.7	0.701	0.062
I	48.2	0.974	0.077	59.6	0.901	0.075
I_{log}	48.7	0.968	0.075	61.2	0.914	0.077
$I_{L/H}$[a]	49.0	0.971	0.077	64.7	0.933	0.083
M	50.7	0.971	0.074	61.6	0.917	0.074
M_{log}[a]	51.4	0.982	0.076	64.2	0.938	0.076

Note: Acc (%) Percentage of simulated trials accepting bioequivalence. K.S. Kinetic sensitivity. S.E. Standard error.
[a] Selected principal metrics.

Table III. Screening of Metrics with Sparse Design Scheme

	$k^o_{aT}/k^o_{aR} = 0.60$			$k^o_{aT}/k^o_{aR} = 2.25$		
Metric	Acc(%)	K.S.	S.E.	Acc(%)	K.S.	S.E.
Id	54.4	0.997	0.074	72.4	1.003	0.075
C_{max}	19.8	0.705	0.054	11.9	0.533	0.052
AUC_p[a]	38.7	0.817	0.061	22.2	0.670	0.062
I	34.2	0.972	0.101	25.9	0.816	0.092
I_{log}	34.4	0.933	0.087	30.6	0.877	0.100
$I_{L/H}$[a]	36.5	0.957	0.099	28.2	0.945	0.155
M	44.3	0.938	0.078	29.0	0.836	0.079
M_{log}[a]	40.9	0.962	0.084	36.5	0.925	0.095

Note: Acc(%) Percentage of simulated trials accepting bioequivalence. K.S. Kinetic sensitivity. S.E. Standard error.
[a] Selected principal metrics.

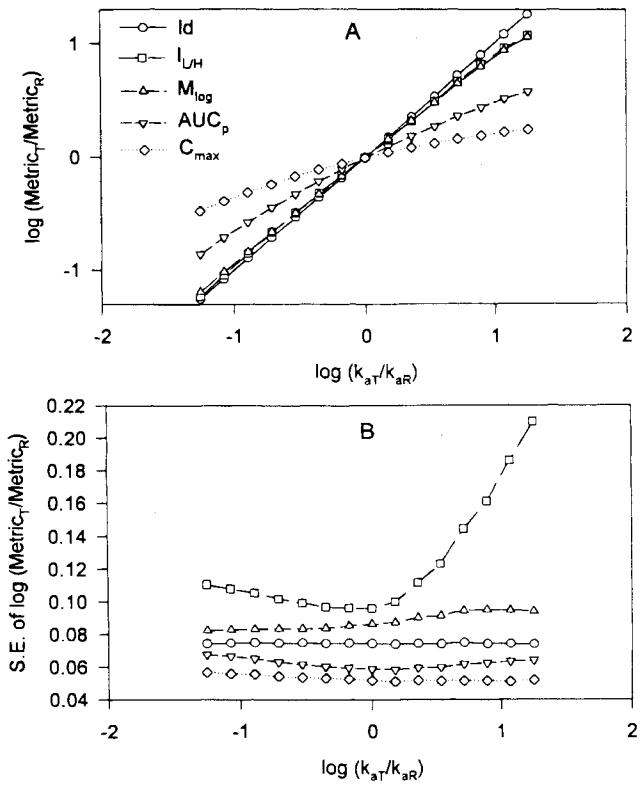

Fig. 5. (A) Kinetic sensitivities and (B) standard errors of ratios of metrics with the sparse design of 9 observations. The interpretation of the diagram is identical to that of Fig. 3.

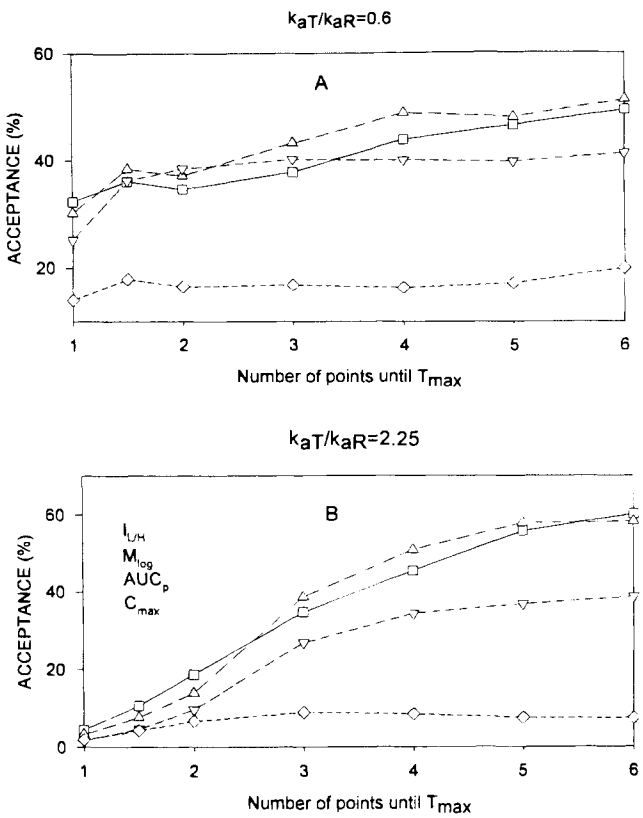

Fig. 6. Effect of the average number of observations, recorded until the population average time of the reference peak ($T^o_{max,R}$), on the percentage of investigations accepting bioequivalence (i.e., the statistical power) by 4 procedures. The simulations were performed by assuming that the ratio of k^o_{aT}/k^o_{aR} was either (A) 0.60, or (B) 2.25.

need not be obtained. The suggested number of observations can serve as a useful guideline for the design of bioequivalence trials.

The present investigation assumed the absence of lag-times during the absorption of drugs. A parallel study has considered the effect of variable lag-times on the effectiveness of assessing bioequivalence in the early phase of an investigation by various methods. The results of this investigation will be presented shortly.

In summary, the three principal procedures evaluated effectively the bioequivalence of concentration-time profiles in their early phases. Consequently, their use for this purpose is recommended. The three methods included the partial AUC, the intercept extrapolating the low-over-high concentrations of the two formulations ($I_{L/H}$), and the modified intercept using log(C/t) values (M_{log}). The two intercept procedures had similar characteristics, with the modified intercept method yielding generally the highest statistical power. Analysis by partial AUC resulted in somewhat lower power under various conditions; the kinetic sensitivity and also the standard error were smaller than the values recorded for the intercept methods.

Table IV. Percentage of Bioequivalence Trials Accepted by Various Methods (the Statistical Power) for Four Kinetic Models

	Flip-flop	Zero-order absorption	2-compartment	
			Model I	Model II
Lower BEL (k^o_{aT}/k^o_{aR})	0.74	0.51	0.55	0.63
Lower k^o_{aT}/k^o_{aR}[a]	0.84	0.60	0.65	0.75
Id	42.4	54.4	55.2	59.6
M_{log}	40.6	50.9	51.4	55.9
$I_{L/H}$	38.4	47.2	48.9	52.7
AUC_p	39.5	54.2	45.7	48.0
C_{max}	27.8	18.2	23.5	27.9
Upper BEL (k^o_{aT}/k^o_{aR})	1.37	2.76	2.26	1.71
Upper k^o_{aT}/k^o_{aR}[a]	1.18	2.30	1.80	1.40
Id	48.8	64.3	82.4	75.2
M_{log}	45.6	64.0	71.5	62.5
$I_{L/H}$	45.4	64.7	71.0	60.9
AUC_p	40.0	52.0	56.9	53.8
C_{max}	24.1	5.3	21.4	27.6

Note: BEL: Bioequivalence limit.
[a] k^o_{aT}/k^o_{aR} ratio at which the metrics were compared.

ACKNOWLEDGMENTS

This investigation was supported, in part, by a contract with the Food and Drug Administration (FDA). The comments and suggestions of members of the FDA Working Group on Metrics (Drs. Mei-Ling Chen (Chair), Alfred Balch, William Gillespie, Yih-Chain Huang and Ajaz Hussain) are acknowledged with appreciation.

REFERENCES

1. M-L. Chen. An alternative approach for assessment of rate of absorption in bioequivalence studies. *Pharm. Res.* **9**:1380–1385 (1992).

2. L. Endrenyi and P. Al-Shaikh. Sensitive and specific determination of the equivalence of absorption rates. *Pharm. Res.* **12**:1856–1864 (1995).
3. P. Macheras, M. Symillides, and C. Reppas. An improved intercept method for the assessment of absorption rate in bioequivalence studies. *Pharm. Res.* **13**:1755–1758 (1996).
4. L. Endrenyi, S. Fritsch, and Y. Wei. Some kinetic and statistical considerations on the evaluation of comparative absorption rates. In I. J. McGilveray, S. V. Dighe, I. W. French, K. K. Midha, and J. P. Skelly (eds.), "Issues in the Evaluation of Bioavailability Data, BioInternational'89", Toronto, pp. 43–48 (1989).
5. F. Y. Bois, T. N. Tozer, W. W. Hauck, M. L. Chen, R. Patnaik, and R. L. Williams. Bioequivalence: performance of several measures of rate of absorption. *Pharm. Res.* **11**:966–974 (1994).
6. A. Rostami-Hodjegan, P. R. Jackson, and G. T. Tucker. Sensitivity of indirect metrics for assessing "rate" in bioequivalence studies—Moving the "goalpost" and changing the "game". *J. Pharm. Sci.* **83**:1554–1557 (1994).
7. L. F. Lacey, O. N. Keene, C. Duquesnoy, and A. Bye. Evaluation of different indirect measures of rate of drug absorption in comparative pharmacokinetic studies. *J. Pharm. Sci.* **83**:212–215 (1994).
8. J. Zha, L. Tothfalusi, and L. Endrenyi. Properties of metrics applied for the evaluation of bioequivalence. *Drug Inf. J.* **29**:989–996 (1994).
9. T. N. Tozer, F. Y. Bois, W. W. Hauck, M-L. Chen, and R. L. Williams. Absorption rate vs. exposure: which is more useful for bioequivalence testing? *Pharm. Res.* **13**:453–456 (1996).
10. L. Endrenyi, F. Csizmadia, L. Tothfalusi, A. H. Balch, and M.-L. Chen. The duration of measuring partial AUCs for the assessment of bioequivalence. *Pharm. Res.* **15**:399–404 (1998).
11. L. Endrenyi, L. Tothfalusi, and J. Zha. Metrics assessing the equivalence of absorption rates and concentration profiles. In K. K. Midha, and T. Nagai (eds.), "F.I.P. Bio-International'96: Bioavailability, Bioequivalence, and Pharmacokinetic Studies", Academic Societies Japan, Tokyo, pp. 169–180 (1996).
12. D. J. Schuirmann. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J. Pharmacokin. Biopharm.* **15**:657–680 (1987).
13. L. Tothfalusi and L. Endrenyi. Without extrapolation, C_{max}/AUC is an effective metric in investigations of bioequivalence. *Pharm. Res.* **12**:937–942 (1995).