Sensitive and Specific Determination of the Equivalence of Absorption Rates

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Purpose. To develop a new method for the direct, sensitive evaluation of the equivalence of absorption rates in linear kinetic systems.
Methods. Concentrations are obtained before the earlier peak. Ratios of concentrations adjusted for the corresponding ratio of AUCs (area under the curve contrasting plasma concentration with time), or their logarithm, are extrapolated by linear regression to the time of drug administration. The intercept estimates the ratio of absorption rate constants (k_a), or its logarithm.
Results. The intercept metric assesses the equivalence of absorption rates with very favourable characteristics. The metric reflects the k_a-ratio specifically (i.e., not affected by other kinetic parameters), is approximately linear to it, exhibits high kinetic sensitivity and excellent statistical properties. With many observations, the intercept metric has near-ideal features, including high power for determining bioequivalence and the ability to detect a 25% difference between k_a values. With only 3 or 4 measurements before the earlier peak, the performance of the metric depends on the preset regulatory conditions. Reasonably good power is noted if the bioequivalence limits determine a 50% difference between two metrics and, approximately, between two k_a values. The intercept metric shows very high power with a wider bioequivalence range. The power declines only moderately with increasing intraindividual variation of k_a. The equivalence of absorption rates is assessed with much higher power by the intercept metric than by C_{max}.
Conclusions. The excellent kinetic and statistical properties of the intercept metric enable the specific and sensitive determination of the equivalence of absorption rates.

KEY WORDS: absorption rate; bioequivalence; sensitivity; specificity; statistical power.

INTRODUCTION

The assessment of bioequivalence currently requires that both the rates and extents of drug absorption of the contrasted drug products should be closely similar. There is general, internationally harmonized consensus on regulatory criteria for the equivalence of extents of absorption (1,2). Thus, as the implementation of the two one-sided tests procedure (3), the 90% confidence limits obtained from the logarithmically calculated average of individual AUC-ratios, i.e., for their geometric mean, should be between 0.80 and 1.25 (1). [AUC: area under the curve contrasting plasma concentration with time.]

There are no similar agreements on standards for the comparison of absorption rates. Geometric means of individual C_{max}-ratios are often applied as measures of comparative absorption rates. [C_{max}: maximum plasma concentration.] However, various regulatory agencies apply widely differing quantitative criteria even if all of them are based on the geometric means of C_{max}-ratios.

In part, quantitative properties of the C_{max}-ratio are substantially unclear and uncertain. Moreover, it is increasingly recognized that the C_{max}-ratio has unfavorable characteristics for the assessment of bioequivalence (4–10). Metrics should reflect specifically the kinetic quantity which they are expected to represent, they should be related linearly to it, should have high kinetic sensitivity and low statistical responsiveness (8,9). For example, AUC represents the extent of absorption in an ideal manner (4,8,9,11). In contrast, the reflection of absorption rates by C_{max}, and of comparative absorption rates by C_{max}-ratios, is far from being ideal (4–10). A method is described in this presentation which estimates ratios of absorption rate constants and determines the equivalence of absorption rates. The resulting metrics have nearly ideal characteristics: they are almost specific, linear, precise and very sensitive.

METHODS

Basis of the Proposed Method

If a drug exhibits first-order absorption and one-exponential disposition then the plasma concentration (C) depends on time (t) according to:

$$C = A \frac{k_a}{k_a - k} (e^{-kt} - e^{-kat}) \qquad (1)$$

Here, k_a and k are first-order absorption and disposition rate constants, respectively, and the coefficient A = F.Dose/V, with F, the "extent of absorption" or, better, the fraction of administered dose reaching the systemic circulation, and V the apparent volume of distribution.

By applying a first-order Taylor expansion around t = 0, the expression at early times is, approximately:

$$C \approx A \frac{k_a}{k_a - k} [(1-kt) - (1-k_at)] \qquad (2)$$

$$= A\, k_a t$$

For two formulations, a test (T) and reference (R) drug product:

$$\frac{C_T}{C_R} \approx \frac{A_T k_{aT}}{A_R k_{aR}}$$

Therefore the ratio of absorption rate constants is, approximately:

$$\frac{k_{aT}}{k_{aR}} \approx \frac{C_T/A_T}{C_R/A_R}$$

The ratio of coefficients can be substituted by the ratio of AUCs:

$$\frac{k_{aT}}{k_{aR}} \approx \frac{C_T/AUC_T}{C_R/AUC_R} \qquad (3)$$

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The validity of this expression improves as the times of obtaining observations become lower and approach zero. It can be demonstrated that Eqs. (2) and (3) can be applied also in more complicated linear kinetic systems (12).

The Proposed Procedure

Fig. 1A illustrates time courses of plasma concentrations for a test and a reference drug product. The two formulations are assumed to have identical kinetics except that the test product has faster absorption.

Ratios of concentrations and logarithms of the ratios are shown in Figs. 1B and 1C, respectively. The ratios decline in the early phase of a study and eventually reach an asymptote provided that the disposition rate constants of the two formulations are the same. Intercepts of the curves at the time of zero are k_{aT}/k_{aR} and $\log(k_{aT}/k_{aR})$, respectively (when $AUC_T = AUC_R$ is assumed).

Therefore, the following procedure is proposed: (a) Measure concentrations C_T and C_R in each subject, after administering the test and reference products, when their values rise, i.e. before the earlier peak; (b) Evaluate AUC_T and AUC_R in each subject from all available observations; (c) Calculate C_T/C_R at each relevant time point before the earlier peak; (d) Estimate the extrapolated intercept, in each subject, by linear regression from either the available $(C_T/AUC_T)/(C_R/AUC_R)$ values or their logarithms; (e) Calculate the average, standard deviation and 90% confidence interval from the individual intercepts within a trial; and (f) Assess whether the confidence interval is within a preset regulatory range. Declare the two drug products to be bioequivalent if their confidence limits are within the preset region, and reject bioequivalence otherwise.

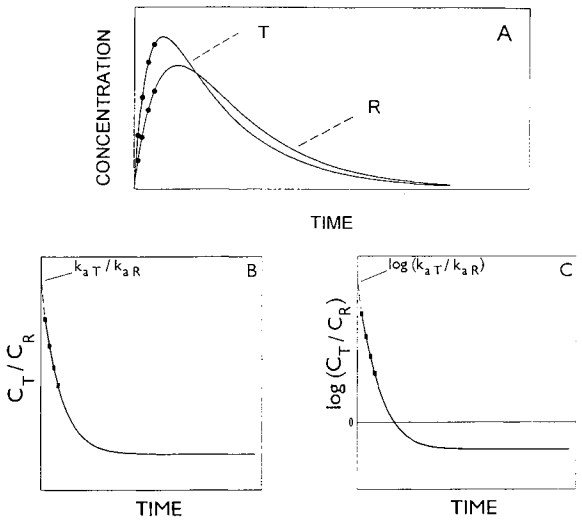

Fig. 1. Background for estimating the ratio of absorption rate constants. A: Time profiles of concentrations in a reference (R) and test (T) drug product. The two formulations have identical kinetics except that the test product has a faster rate of absorption than the reference formulation. Observations taken before the earlier peak are shown. B: Ratio of plasma concentrations in two drug products. Ratios formed from the early observations are extrapolated by linear regression. The intercept estimates the ratio of absorption rate constants. C: Logarithm of the ratio of plasma concentrations. The interpretation is similar to that given for Panel B except that the extrapolated intercept estimates the logarithm of the ratio of absorption rate constants.

Simulation of Bioequivalence Trials

Two-way crossover trials were simulated in which two drug products, reference (R) and test (T), were assumed to be administered on separate occasions to 20 subjects. The sequences of drug administration were allocated randomly.

The simulations considered a kinetic model with first-order absorption and one-exponential disposition (Eq. 1). The population mean parameters for the reference product were set arbitrarily to $A_R = 100$, $k_R = \ln 2$ and $k_{aR} = 5 \ln 2$. Consequently, the time scale was set in terms of the disposition half-life, and $k_{aR} = 5k_R$. The population mean parameters for the test formulation were defined in terms of the mean values of the R-product. Arbitrarily, $A_T = A_R$, and $k_T = k_R$. The ratio of k_{aT}/k_{aR} was gradually increased from the value of 1.0, the condition of true bioequivalence.

In studies assessing the inter- and intraindividual variabilities of parameters, lognormal distributions were assumed. The means were considered to be zero, and the variances (σ^2) were calculated from preset coefficients of variations (CV) by (13):

$$\sigma^2 = \log[(CV/100)^2 + 1]$$

For the evaluation of AUC and C_{max}, the simulated trials were assumed to proceed for 3 disposition half-lives beyond the concentration peak of the reference formulation: 20 readings were arranged at slowly increasing intervals which had a ratio of 1.1 for the consecutive time differences. For the estimation of the intercept metrics, either 20 or 5 or 4 observations were spaced in a similar pattern until the earlier population average peak. For example, 5 observations were set at .164, .344, .542, .760 and 1.000 in terms of the earlier T_{max}. The reading at the true maximum was not used in the regressions and consequently an average of either 19 or 4 or 3 data points were applied for estimating the intercepts. The number of measurements recorded for individuals fluctuated around these numbers. Intercepts were not estimated for subjects who had fewer than two observations available with either formulation, and these individuals were not included in the further calculations. The concentrations were assumed to exhibit lognormal distributions with means of zero and coefficients of variation, in turn, of 5, 15 and 25%.

Performance of Metrics Assessing Bioequivalence: Power Curves

After each simulated trial, the acceptability of bioequivalence was determined by the two one-sided tests procedure (3). In order to make decisions, regulatory criteria had to be first established. Two drug products were judged to be bioequivalent if the 90% confidence interval for the ratio of geometric means of a metric was within preset limits. The limits were symmetrical in the logarithmic scale and therefore reciprocally related without transformation. One of 3 ranges were chosen: either 0.80–1.25 or 0.67–1.50 or 0.30–3.3. The intercept metrics yielded direct measures for the ratios of geometric means. Averages of individual intercepts obtained from logarithmic concentrations ratios were back-

transformed. In the case of intercepts obtained from untransformed concentration ratios, logarithms were calculated before averaging. Standard deviations and averages were estimated. In order to characterize the performance of a metric, power curves were obtained under various conditions. Power curves depict the relationship between the probability of accepting bioequivalence and a changing contrast in a relevant kinetic quantity of the two formulations.

One hundred crossover trials were simulated under each combination of kinetic and statistical conditions, and the number of trials was recorded in which bioequivalence was accepted. The proportion of trials accepting bioequivalence estimated the corresponding probability. The ratio of absorption rate constants, k_{aT}/k_{aR}, was gradually increased from 1.0, from true equivalence to rising deviations from this condition.

Ideally, with small parameter variabilities and measurement errors, bioequivalence is declared as long as the contrast of metrics (almost) does not reach one of the preset regulatory limits. Beyond the limit, lack of bioequivalence is stated. Consequently, the power curve shows a sharp decline between statements in favor and against the applicability of bioequivalence and thereby enables a clear decision between the two alternatives. The relationship between the preset deviation (e.g., 25%) in the metric and the ratio of the kinetic quantities (e.g., k_{aT}/k_{aR}) at which the break in the power curve can be seen, defines the *kinetic sensitivity* of the metric (8,9). In the presence of parameter variabilities and/or observational errors, the power curve descends gradually. The deviation of power from its ideal value, under a given condition, measures the *statistical responsiveness* of the metric to underlying sources of variation (8,9). High kinetic sensitivity and low statistical responsiveness are favourable properties of a metric (8,9).

The (alternative) hypothesis of accepting bioequivalence should have a low probability at the regulatory limits where the two drug products are in fact substantially different. This probability is the *consumer risk* (14) which has been traditionally set at 5%. On the other hand, if the two formulations are truly equivalent then an incorrect declaration of inequivalence is the *producer risk*. This should be minimized while a fixed consumer risk is maintained.

Power curves will be presented for the intercept metrics under various conditions.

Equivalence of the Intercept Metrics with a Large Number of Observations

Figure 2 shows power curves for the assessment of relative absorption rates by the intercept method (the extrapolated intercept of either the untransformed or logarithmic ratio of concentrations of the test and reference products) when 19 simulated data points were available before the earlier peak. A narrow regulatory criterion was applied in the simulations. Bioequivalence was stated in a simulated trial as long as the 90% confidence limits for the extrapolated mean concentration ratio was within 0.80 and 1.25.

Fig. 2 illustrates that, with small measurement errors, a clear regulatory decision point is seen at a 25% difference between absorption rate constants. (The decision point separates statements made in favour and against the applicability of bioequivalence.) Consequently, under these conditions, the metrics have very high kinetic sensitivity: a 25% difference in the underlying kinetic parameter elicits a 25% difference in the metrics.

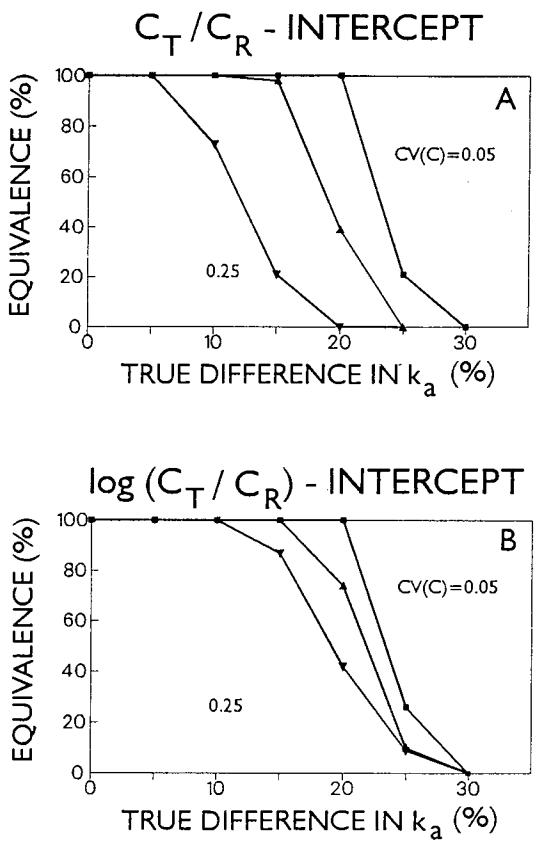

Fig. 2. Power curves for the determination of the equivalence of the intercept metrics when many observations are available (an average of 19 measurements before the earlier peak). Intercepts were calculated from A: the plasma concentration ratios (C_T/C_R), or B: their logarithms ($\log(C_T/C_R)$). A narrow regulatory criterion was assumed with bioequivalence limits of 0.80–1.25 for the intercept metrics. Consequently, the figure illustrates the high kinetic sensitivity of the metrics: at small measurement errors, a 25% deviation is evoked by a 25% difference in the k_a-ratio. The statistical responsiveness of the metrics is satisfyingly low.

With increasing observational errors, the power of the decisions deteriorates. However, the rate of reduction in power is moderate. It is compatible with the characteristics of an ideal metric, AUC representing the extent of absorption (4,11). Better behavior is observed with the intercept of logarithmic than with untransformed concentration ratios (Fig. 2). Altogether, the intercept metrics exhibit, with a large number of observations, high kinetic sensitivity and low statistical responsiveness.

Equivalence of the Intercept Metrics with a Small Number of Observations

Figures 3 and 4 present power curves for the evaluation of equivalence by the intercepts of both untransformed and logarithmic concentration ratios when only 4 or 3 observations respectively, are obtained before the earlier peak. Re-

sults obtained with 3 regulatory conditions are shown in both diagrams.

When the 90% confidence limits for the geometric averages of individual intercepts are assumed to be within the narrow bioequivalence range of 0.80–1.25 then the power of bioequivalence determination is generally low and inadequate (Panels A and B in Figs. 3 and 4). When the regulatory limits are relaxed to the range of 0.67–1.50 then the power of bioequivalence determination shows moderate reduction with increasing observational errors, especially if an average of 4 readings can be obtained before the earlier peak (Panels C and D in Figs. 3 and 4). The pattern of power curves is rather similar to that shown for C_{max} with a much wider, less sensitive regulatory region (4,5,9).

The final bioequivalence range for the intercept metrics was assumed to be as wide as 0.30–3.3 (Panels E and F in

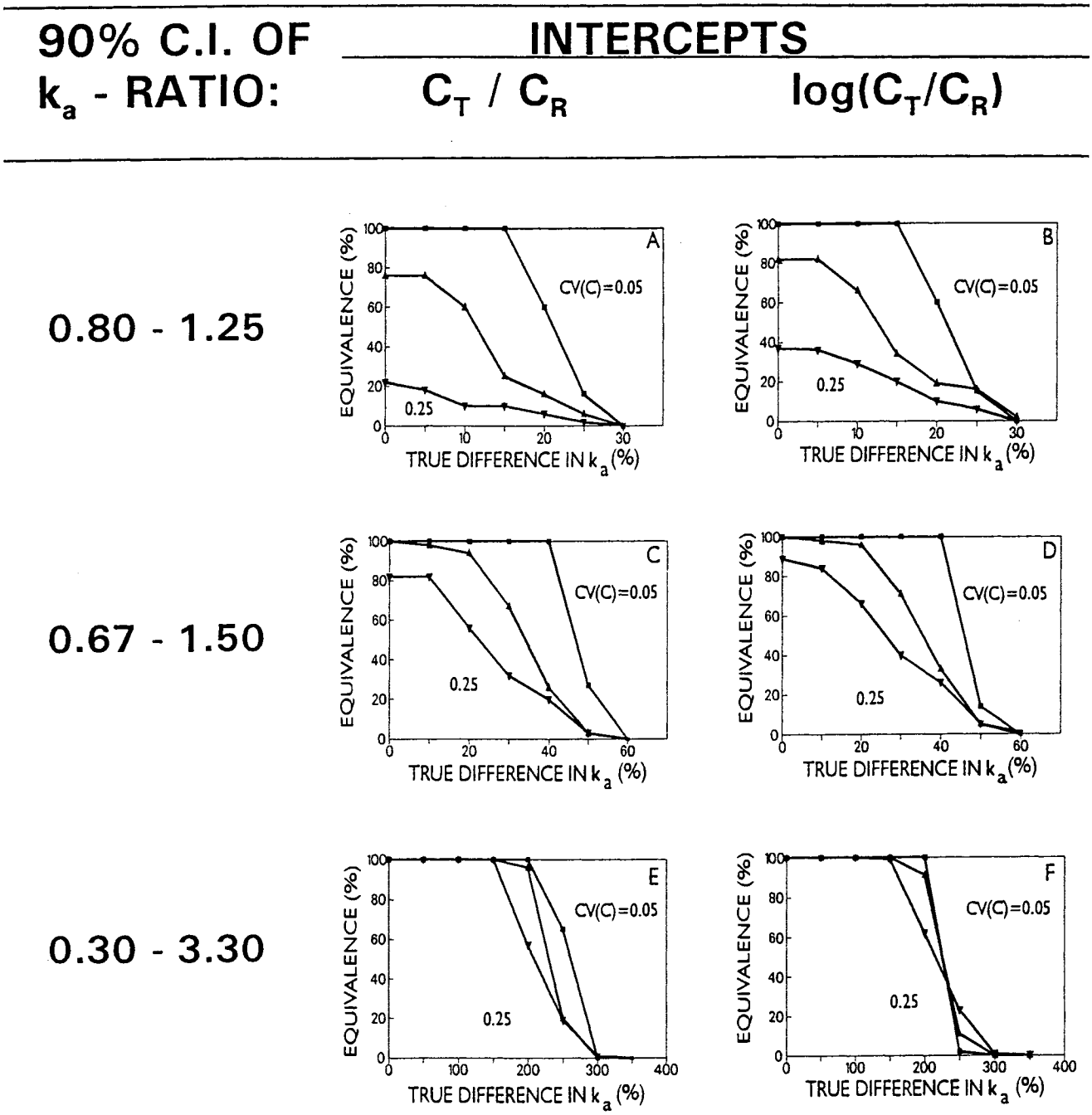

Fig. 3. Power curves for the determination of the equivalence of the intercept metrics when, on average, 4 observations are available before the earlier peak. The intercepts were estimated from A,C,E: untransformed, and B,D,F: logarithmic concentration ratios. The regulatory conditions assumed bioequivalence limits for the estimated metrics of A,B: 0.80–1.25; C,D: 0.67–1.50; E,F: 0.30–3.3. The statistical responsiveness under the three regulatory conditions was poor, reasonable, and excellent, respectively. At small measurement errors, the k_a-ratio separating decisions in favour and against bioequivalence agreed closely with the preset regulatory condition for the metrics (e.g., 3.3). Consequently, the intercept metrics were approximately linear with respect to the k_a-ratio and exhibited high kinetic sensitivity.

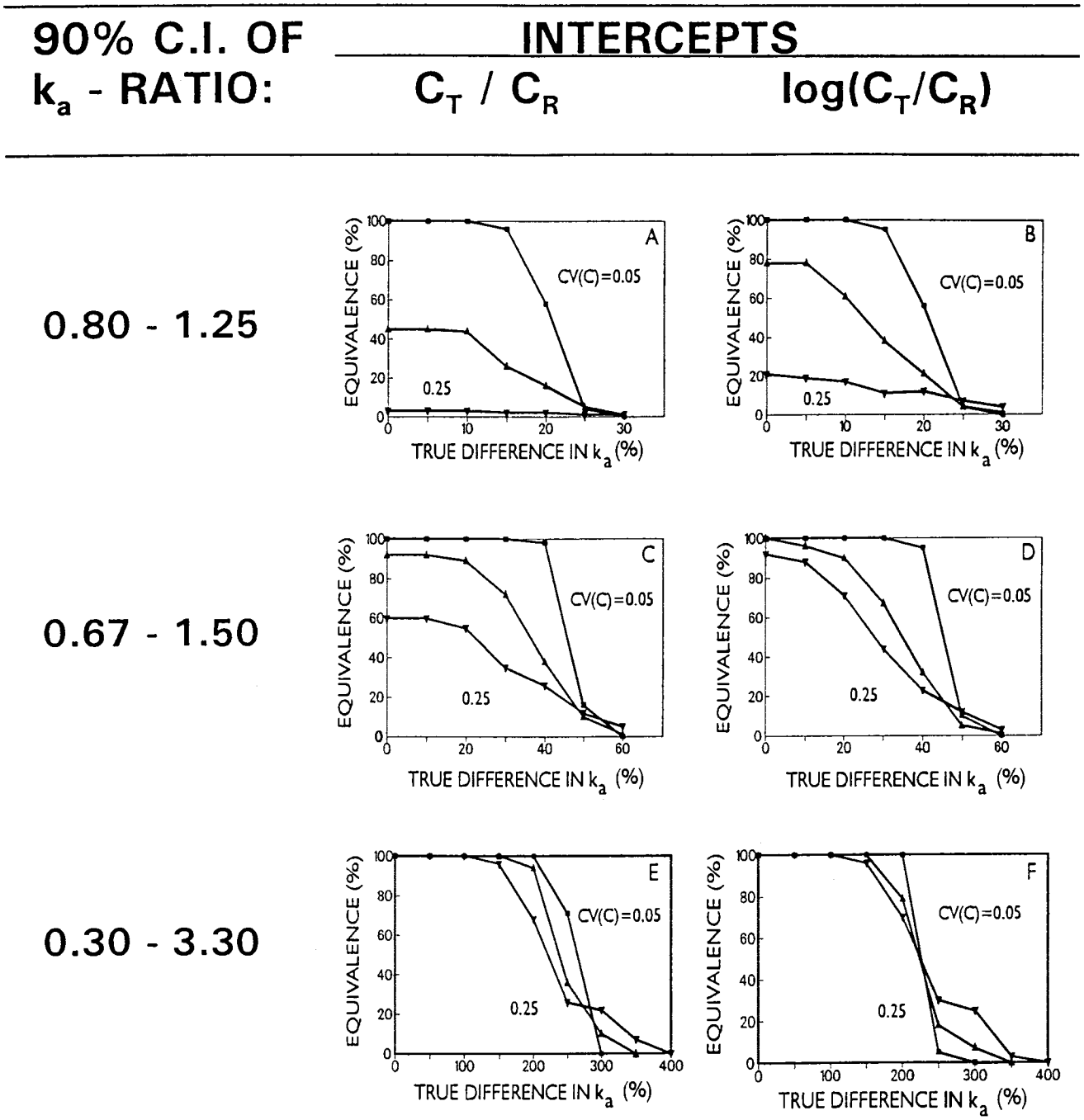

Fig. 4. Power curves for the determination of the equivalence of the intercept metrics when, on average, 3 observations are available before the earlier peak. The arrangement of the diagrams is identical to that given for Fig. 3. The interpretations are also similar.

Figs. 3 and 4). The range is identical to that evoking, with small observational errors, a 25% difference in C_{max}. Therefore, the results in Panels E and F of Figs. 3 and 4 can be directly compared with those reported for a 25% difference between C_{max} values, (7,8,12). With increasing measurement errors, the power of the intercept metrics deteriorates much more slowly than that of the C_{max}-ratio. Consequently, the intercept metrics show very low statistical responsiveness. The intercept metric based on logarithmic concentration ratios has generally higher power and lower statistical responsiveness than that obtained from untransformed concentration ratios. For the intercept metrics, the decision point separating, in terms of the k_a-ratio, statements in favour and against the applicability of bioequivalence is approximately identical, at small measurement errors, with the preset regulatory criterion. Consequently, the metrics exhibit both linearity and high kinetic sensitivity.

Effect of Intrasubject Variability of k_a

The simulations were repeated by assuming two levels of intraindividual variability for the absorption rate constant.

$CV(k_a)$ = 20 and 40% could correspond to moderate and high variabilities, respectively.

Figures 5 and 6 present power curves with intermediate (0.67–1.50) and wide (0.30–3.3) regulatory ranges, respectively, with an average of only 3 observations before the earlier peak. Consequently, the illustrations in Fig. 5 should be compared with those given in Panels C and D of Fig. 4, whereas the diagrams in Fig. 6 should be contrasted with Panels E and F of Fig. 4.

The power of assessing the equivalence of k_a in two drug products is seen to decrease moderately with increasing intraindividual variability of k_a when the regulatory region has an intermediate width (Fig. 5). Only a slight decrease of the power can be observed when the regulatory range is wide (Fig. 6).

DISCUSSION

Properties of the Intercept Method

A new approach is proposed for assessing the equivalence of absorption rates and for estimating ratios of absorption rate constants. It is suggested that either untransformed or logarithmic ratios of concentrations of two drugs or drug products, adjusted by the respective AUCs, be recorded during the period of rising measurement values, before the earlier peak, and that the intercept of these ratios be estimated from extrapolating by simple linear regression. The intercept directly estimates the ratio of absorption rate constants, or their logarithm, and can be used to evaluate their equivalence.

The intercept metrics have remarkably favourable properties for assessing the equivalence of absorption rates. They are *specific:* the intercept estimates the k_a-ratio and, consequently, differences in the intercept reflect only contrasts of k_a-ratios but not of other kinetic quantities. The intercept is, in its untransformed form, not only *linear* with but proportionate to the k_a-ratio. As a result, the metrics exhibit *high kinetic sensitivity* to the underlying kinetic parameter.

In the ideal case when many observations are available until the earlier peak and with a very narrow regulatory con-

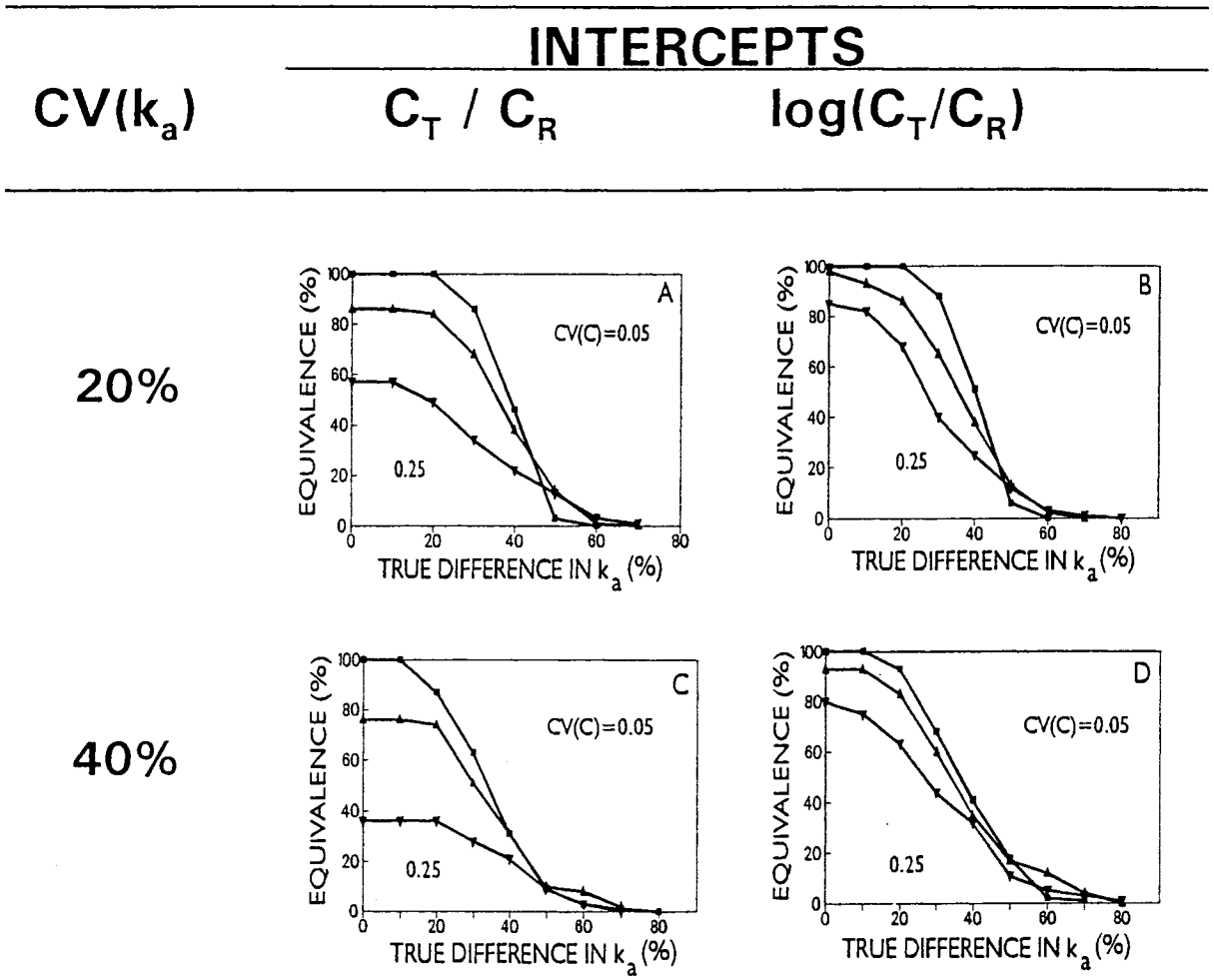

Fig. 5. Effect of intraindividual variability of k_a on the power of determining the equivalence of the intercept metrics. 3 observations were, on average, simulated before the earlier peak. The regulatory condition assumed bioequivalence limits of 0.67–1.50 for the estimated metrics. The intercepts were estimated from A,C: untransformed, and B,D: logarithmic concentration ratios. The intrasubject variation of the absorption rate constant was $CV(k_a)$ = A,B: 20%; C,D: 40%. Intraindividual variation of k_a had only moderate effect on power (compare also with Figs. 4C and 4D).

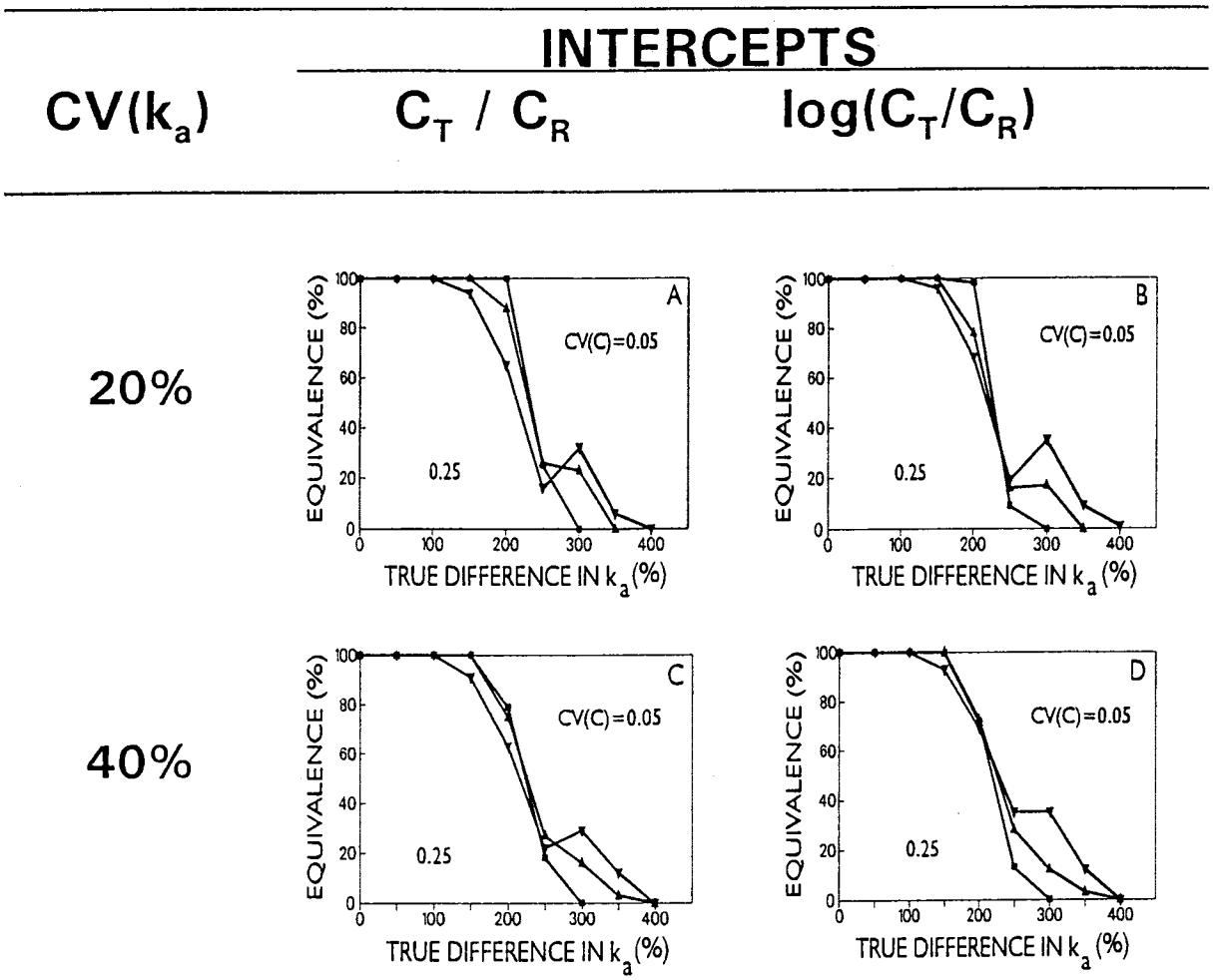

Fig. 6. Effect of intraindividual variability of k_a on the power of determining the equivalence of the intercept metrics. The regulatory condition assumed bioequivalence limits of 0.30–3.3 for the estimated metrics. Other conditions of the simulations and the arrangement of the diagrams were identical to those given for Fig. 5. Intraindividual variation of k_a has only small effect on power (compare also with Figs. 4E and 4F).

dition of 0.80–1.25 for the intercept metric, the power of bioequivalence determination declines at a moderate rate with increasing measurement errors. Thus, the *statistical responsiveness* of the intercept metric to errors and parameter variabilities is also quite small. It is in fact comparable to the statistical responsiveness shown by AUC, an ideal metric.

When only an average of 3 or 4 observations can be obtained before the earlier peak then the power of determining the equivalence of absorption rates, and with it the statistical responsiveness, becomes rather poor with the tight regulatory condition of 0.80–1.25. However, when the regulatory limits are widened to a still narrow range of 0.67–1.50 then the responsiveness improves substantially: its pattern becomes similar to that shown by AUC with a narrower regulatory range. Finally, if the regulatory limits are widened even farther to 0.30–3.3, the condition yielding a 25% difference in C_{max}, then the statistical responsiveness is very small and the power of determining bioequivalence remains very high over a wide range of conditions.

The illustrations shown in this paper demonstrate, for the sake of simplicity, properties of metrics which are obtained from extrapolated intercepts of C_T/C_R ratios or their logarithms. In the proposed procedure each concentration should be divided by the respective AUC. Concentrations divided by AUC retain the effectiveness of unadjusted concentrations (12). The adjustment by AUC is analogous to the suggested use of C_{max}/AUC as an indirect metric for absorption rates (5,10,15). This ratio-measure is more specific than C_{max} since it does not depend on the extent of absorption.

The behaviour of statistical power and responsiveness depends strongly on the regulatory limits for bioequivalence (9). This illustrates a consequence of "moving the goalposts", the bioequivalence limits (7). The results demonstrate that the "goalposts" for a metric should be established by taking into account both its kinetic sensitivity and statistical responsiveness (9). The intercepts calculated by the extrapolation of logarithmic concentration ratios have generally more favourable properties than those obtained from the untransformed ratios.

Conditions and Limitations for Using the Intercept Metrics

The proposed method is useful for the estimation of ratios of first-order absorption rate constants and for the

determination of their possible equivalence. The results demonstrate that the intercept metric can be usefully applied when an average of either 3 or 4 measurements can be obtained before the earlier peak. Four observations are generally much more effective. The condition may impose constraints with drugs which are rapidly absorbed. With extended-release formulations, the requirements of the method are usually amply satisfied. Disposition is not limited to the one-exponential form and can take any complexity of a linear system. This is reasonable since very soon after the administration of a drug, its absorption dominates other kinetic processes. As a result, the intercept metrics capture the initial kinetics in a system.

The approach will have to be modified in the future to accommodate zero-order absorption. Several metrics (e.g., C_{max}) share this difficulty. Its source is that terms for both the extent and zero-order rate of absorption form a product in the coefficient A. Their resolution requires information additional to that available from single drug administration. The possible usefulness of the proposed procedure with nonlinear disposition kinetics will also be explored in the future.

The conditions and limitations for applying the intercept metrics will have to be validated and confirmed in future investigations. Computer simulations covering a wide range of modeling and experimental conditions, similar to those performed by Bois et al. (6,11) and Tothfalusi and Endrenyi (15), and the analysis of available measurements will be useful for this purpose.

Suggested Regulatory Environment and Conditions

Comparison of Absorption Rates or Concentration Profiles?

The results can be viewed in two regulatory contexts. On the one hand, the intercept metrics provide a direct measure of absorption rates with very favourable, almost ideal properties. In an alternative regulatory context, the intercept metrics can be considered to discriminate not merely between features of a kinetic parameter, the absorption rate constant, but between those of the time profiles of concentrations of the two formulations. In this more general view, overlap of the profiles demonstrates the equivalence of two drug products. The excellent kinetic and statistical properties of the intercept metrics commend their application also in the wider regulatory context. Furthermore, their kinetic and statistical characteristics enable the judicious choice of bioequivalence limits.

Regulatory Ranges

Let us consider the narrow regulatory view when the metrics represent a kinetic parameter, the absorption rate constant in this case. We could maintain, approximately, the regulatory criteria which have traditionally indicated the equivalence of C_{max} in two formulations. For example, a decision point for the applicability bioequivalence can be a 25% difference between the C_{max} values recorded for the two drug products as is the case in Canada. Under the investigated kinetic conditions, this corresponds to a ratio of absorption rate constants, $k_{aT}/k_{aR} = 3.3$. The initially chosen bioequivalence limits for the intercept metrics could then be 0.30–3.3.

Thus, the k_{aT}/k_{aR} ratio separating decisions in favour and against bioequivalence depends on the chosen regulatory criterion (9). Moreover, this limiting k_a-ratio depends also on the quantitative kinetic conditions (7–9) which are generally known only with uncertainty. Consequently, there is considerable spread in the k_a-ratio which corresponds to a given regulatory criterion for C_{max}. The uncertainty is a consequence of the nonlinearity of C_{max} with respect to the kinetic parameter k_a. On the whole, the regulatory conditions for single drug administration, based on C_{max}, correspond to a 2–5 fold ratio of the contrasted absorption rate constants (9).

Regulatory Choices for Comparing Absorption Rates by the Intercept Metrics

The near-linearity of the intercept metrics strongly enhances the interpretation of the regulatory criterion based on them. Thus, if the regulatory condition is set at a value of the intercept metrics of, say, 3.3, then this corresponds to a k_a-ratio of approximately 3.3. Moreover, this relationship is almost unaffected by the kinetic conditions, notably by the k_a/k-ratio. If the regulatory choice is then a wide bioequivalence range, say 0.30–3.3, to correspond approximately to current criteria for C_{max}, then the intercept metrics exhibit very low statistical responsiveness and enable to make clear decisions about the equivalence of absorption rates. Alternatively, the regulatory choice could be a narrower bioequivalence range, say 0.50–2.0 or 0.67–1.50. The statistical responsiveness would be moderately low, similar to that shown by AUC with respect to the extent of absorption, and thus probably acceptable. The narrower bioequivalence limits permit a stricter, more sensitive discrimination between the absorption rates of two drug products. The possible usefulness of this course is a matter of judgment.

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