Sensitivity of Empirical Metrics of Rate of Absorption in Bioequivalence Studies

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Purpose. The sensitivity and effectiveness of indirect metrics proposed for the assessment of comparative absorption rates in bioequivalence studies [C_{max}, T_{max}, partial *AUC* (AUC_p), feathered slope (SL_f), intercept metric (I)] were originally tested by assuming first-order absorption. The present study re-evaluates their sensitivity performances using the more realistic inverse Gaussian (IG) model characterizing the input process for oral drug administration.

Methods. Simulations were performed for both the first-order or exponential model (EX) which is determined by only one parameter, the mean absorption time ($MAT = 1/k_a$), and the IG model, which additionally contains a shape parameter, the relative dispersion of absorption time distribution (CV_A^2). Kinetic sensitivities (KS) of the indirect metrics were evaluated from bioequivalence trials (error free data) generated with various ratios of the true parameters (*MAT* and CV_A^2) of the two formulations.

Results. The behavior of the metrics was similar with respect to changes in *MAT* ratios with both models: KS was low with C_{max}, moderate with SL_f and AUC_p, and high with I and T_{max} following correction for apparent lag time (T_{lag}). Changes of the shape parameter CV_A^2, however, were not detectable by C_{max}, T_{max}, SL_f, and AUC_p. Changes in both *MAT* and CV_A^2 were well reflected by I with CV_A^2-ratio > 1. I exhibited approximately full KS also with CV_A^2-ratio < 1 when a correction was first applied for the apparent lag time.

Conclusions. The time profile of absorption rates is insufficiently characterized by only one parameter (*MAT*). Indirect metrics which are sensitive enough to detect changes in the scale and shape of the input profile could be useful for bioequivalence testing. Among the tested measures, I is particularly promising when a correction is applied for T_{lag}.

KEY WORDS: bioequivalence; absorption rate; extended-release; mean absorption time; relative dispersion.

INTRODUCTION

The role of secondary metrics for the assessment of bioequivalence, which accounts for the influence of the rate of absorption, or more generally the shape of the concentration-time profile in the early phase, has been of interest in recent years. The sensitivity of indirect metrics to changes in the shape of the early concentration profile was tested in simulation studies assuming first-order absorption and taking the absorption rate constant k_a as a "gold standard" for defining the initial rate of absorption (1–8). However, in contrast to the extent of absorption, the profile of absorption rate often cannot be described by only one parameter.

Tozer *et al.* (5) proposed the bioequivalence of two drug products could be evaluated by comparing three measures of drug exposure. One of these would be an index of early exposure and would characterize the early phase of the concentration-time curves. The idea was incorporated into a recently published draft guidance of the FDA (9).

Thus, two questions arise. First, do the results obtained for the kinetic sensitivity of indirect metrics on the basis of the most simple absorption model apply also under other conditions of absorption, e.g., to extended-release dosage forms? (The first-order absorption model implies exponentially distributed absorption times and is abbreviated as the EX model.) Second, do the indirect metrics also account for other changes in the absorption process (i.e., in the resulting oral concentration time profile) than those described by k_a?

It is the purpose of this paper to study the kinetic sensitivities of previously proposed indirect metrics by using a more flexible absorption model which has been successfully applied to sustained release formulations (10,11); the model was also capable to fit literature data (12) of three oral chlorprothixene formulations (solution, suspension, and tablet) (unpublished results). This input model assumes an inverse Gaussian distribution of the absorption times (IG model). It contains two parameters, the mean absorption time (*MAT*) which corresponds to k_a of the first-order model ($MAT = 1/k_a$) and acts as a scale parameter of the input function, and the relative dispersion of the absorption times (CV_A^2) which is a shape parameter of the absorption rate vs. time profile of the IG model. Interestingly, the latter also accounts for the problem of an apparent lag time in the concentration-time profiles of drugs following oral administration which is conventionally treated as a separate case of the EX model, the first-order absorption with lag time (13).

METHODS

Exponential and Inverse Gaussian Models

The parameters bioavailability (F) and mean absorption time (*MAT*) completely determine the exponential density (EX) characterizing first-order absorption ($MAT = 1/k_a$). In the presence of a lag time (T_{lag}) for absorption, the absorption density with the EX model becomes:

$$f_A(t) = \begin{cases} 0 & t < T_{lag} \\ F\ MAT^{-1} e^{-(t-T_{lag})/MAT} & t \geq T_{lag} \end{cases} \qquad (1)$$

The use of the inverse Gaussian density as a model for the assessment of drug absorption has been described in detail elsewhere (10). The inverse Gaussian (IG) density

$$f_A(t) = F \sqrt{\frac{MAT}{2\mu CV_A^2 t^3}} \exp\left[-\frac{(t - MAT)^2}{2CV_A^2\ MAT\ t} \right] \qquad (2)$$

contains an additional parameter, the relative dispersion (CV_A^2) in the distribution of absorption times. CV_A^2 describes the shape of the absorption rate vs. time profile: equation 2 attains its maximum at the time $T_{A,max}$, and the ratio $T_{A,max}/MAT$ is completely determined by CV_A^2 (10). While for the EX model,

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the absorption rate decreases monotonically starting with its maximum value at the time of zero, the IG density is a unimodal function, where the absorption rate first increases and then declines. Figure 1 demonstrates the IG absorption density can be approximated by the EX model with a lag time. Note that MAT_{IG} of the IG model can be in this case approximated by $MAT_{EX+Tlag} = 1/k_a + T_{lag}$.

Assuming, as in most comparable studies, a monoexponential disposition curve following an iv dose (D_{iv}) of the drug, the concentration is:

$$C_{iv}(t) = Ae^{-\lambda t} \tag{3}$$

where λ is the disposition rate constant. The Laplace transform of the concentration-time curve after an oral dose (D_{po}) is then obtained as a product of the absorption and disposition function (Laplace transforms of equations 2 and 3) (10), i.e.:

$$\hat{C}_{po}(s) = F\frac{D_{po}}{D_{iv}} \exp\left\{\frac{1}{CV_A^2} - \left[\frac{MAT}{CV_A^2/2}\left(s + \frac{1}{2MATCV_A^2}\right)\right]^{1/2}\right\} \frac{A}{s+\lambda} \tag{4}$$

Numerical inverse Laplace transformation is applied to convert equation 4 into the time domain. [For the EX model (Eq. 1) a well-known closed form solution (the Bateman function) is available in the time domain.]

Figure 2 illustrates properties of the inverse Gaussian model, the effect of *MAT* and CV_A^2 on concentration-time curves. For $CV_A^2 \leq 1$ the apparent lag time increases with decreasing values of CV_A^2 (Fig. 2B). This is in accordance with the fact that in the limiting case of $CV_A^2 \to 0$, the IG model approaches a pure lag-time system where the input impulse is simply delayed by *MAT* [$f_A(t) \to F\delta(t - MAT)$, δ(t) is the delta function)]. The departure of the IG from the EX density shows a minimum at $CV_A^2 = 1.38$ (14). Thus, it is not surprising the differences between concentration-time curves of the two models may hardly be detectable in practice (Fig. 1). However, the underlying discontinuous profile of the EX + T_{lag} model is less realistic than that predicted by the IG model since, for oral formulations (and especially for retard formulations), the input rate to the systemic circulation cannot be maximal at the time of zero (e.g., 15). Because of this inherent property of the IG model (which is especially pronounced for $CV_A^2 < 1$), the apparent lag time in a calculated concentration-time curve has to be taken as much into account as in the assessment of real data; otherwise, indirect metrics originally tested using the EX model would fail or lead to biased estimates due to the misspecification of the model (13).

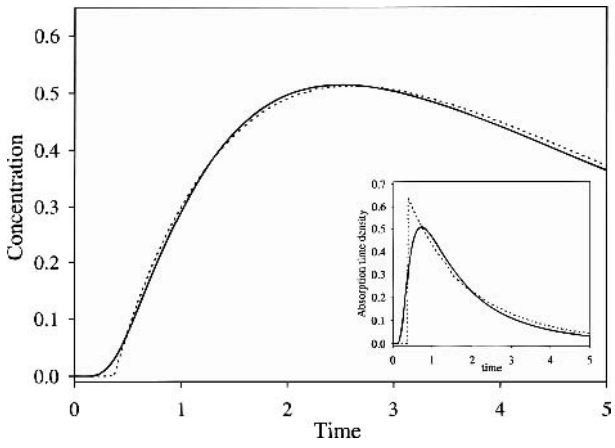

Fig. 1. Concentration vs. time curves simulated for IG absorption (*MAT* = 2; $CV_A^2 = 0.8$) (solid curve), and first-order absorption (k_a = 0.64) with a lag time (T_{lag} = 0.37) (dashed curve) assuming monoexponential disposition (λ = 0.25). The insert shows the corresponding absorption rate vs. time profiles.

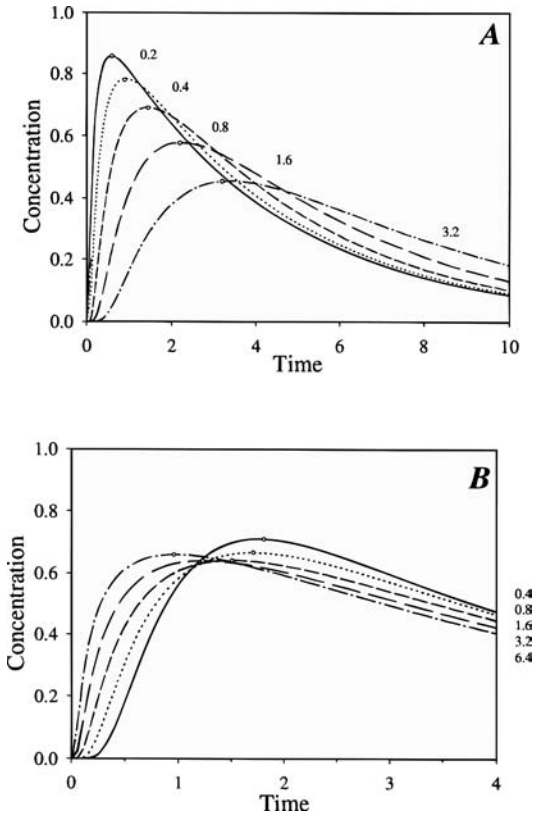

Fig. 2. Concentration vs. time profiles simulated assuming monoexponential disposition (λ = 0.25) and (A): the IG absorption model with $CV_A^2 = 1$ and *MAT* = 0.2, 0.4, 0.8, 1.6 and 3.2; (B): IG model with *MAT* = 1 and CV_A^2 = 0.4, 0.8, 1.6, 3.2, and 6.4.

Data Points for Analysis

Oral plasma concentrations were set by using equation 4 with λ = 0.2 h^{-1}, *F* = 0.8, and unit doses. The values of *MAT* and CV_A^2 were set from 0.2 to 2 h and from 0.5 to 5, respectively, in geometric series. Plasma concentrations were calculated at the following time points: .15, .30, .45, .6, .8, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0,3.5, 4, 5, 6, 8 hours. This experimental design gave more emphasis to the early phase of the curve following drug administration. The parameter values of the reference drug were placed at the center of the examined intervals, i.e., at MAT_R = 0.73 h and $CV_{A,R}^2 = 1.88$.

Calculation of Indirect Metrics

The following metrics were estimated for the rate of drug absorption: C_{max} and T_{max} were observed directly from the data.

The partial AUC (AUC_p) was the area under the curve from zero to T_{max} of the reference or test formulation, whichever occurred earlier (16). The feathered slope parameter (SL_f) was calculated as follows. After fitting a straight line to the last four log-transformed concentration points, concentration values along that line were calculated at the first four time points of the sampling scheme. The so-called feathered line was then obtained by fitting again log-transformed differences between the extrapolated and recorded concentrations, and the negative slope represented the metric SL_f.

The intercept metric is defined in two ways (3). I_{lin} calculates the concentration ratios (C_T/C_R) in the early phase of a study and extrapolates them to the time of zero. $Exp(I_{log})$ is the anti-log of the extrapolated $\log(C_T/C_R)$ values. The modified intercept metrics M_{lin} and $Exp(M_{log})$ are defined analogously with the difference that the underlying extrapolated functions are the $C(t)/t$ and $\log[C(t)/t]$ values, respectively, in the early phase (17). The intercept metrics were originally defined and tested for $C(t)$ curves with a decreasing slope in their ascending segment (until the slope becomes zero at T_{max}). These metrics must fail for curves where this slope first increases and then decreases as predicted by the IG model, especially when $CV_A^2 < 1$ (see the discussion of the apparent lag time problem above). The method of Csizmadia and Endrenyi (13) was used to correct the data for the apparent lag time before calculating the intercept metrics.

Kinetic Sensitivity of Metrics

The metrics were calculated from error-free data since the goal of the study was the evaluation of the kinetic sensitivity of the measures (18). The results are presented in form of sensitivity curves which contrast, in a double-logarithmic plot, the ratio of the metrics calculated for the test (T) and reference (R) formulations as a function of the corresponding ratio of the parameters of the underlying absorption model *MAT* and CV_A^2. Ideally, with full kinetic sensitivity, a metric (or its ratio) increases or decreases proportionally to an underlying kinetic quantity (or its ratio). Consequently, the slope of the double-logarithmic plot is either 1 or −1. A metric with low sensitivity has a smaller slope (in absolute value). The slopes for supersensitive metrics are larger than 1 (in absolute value).

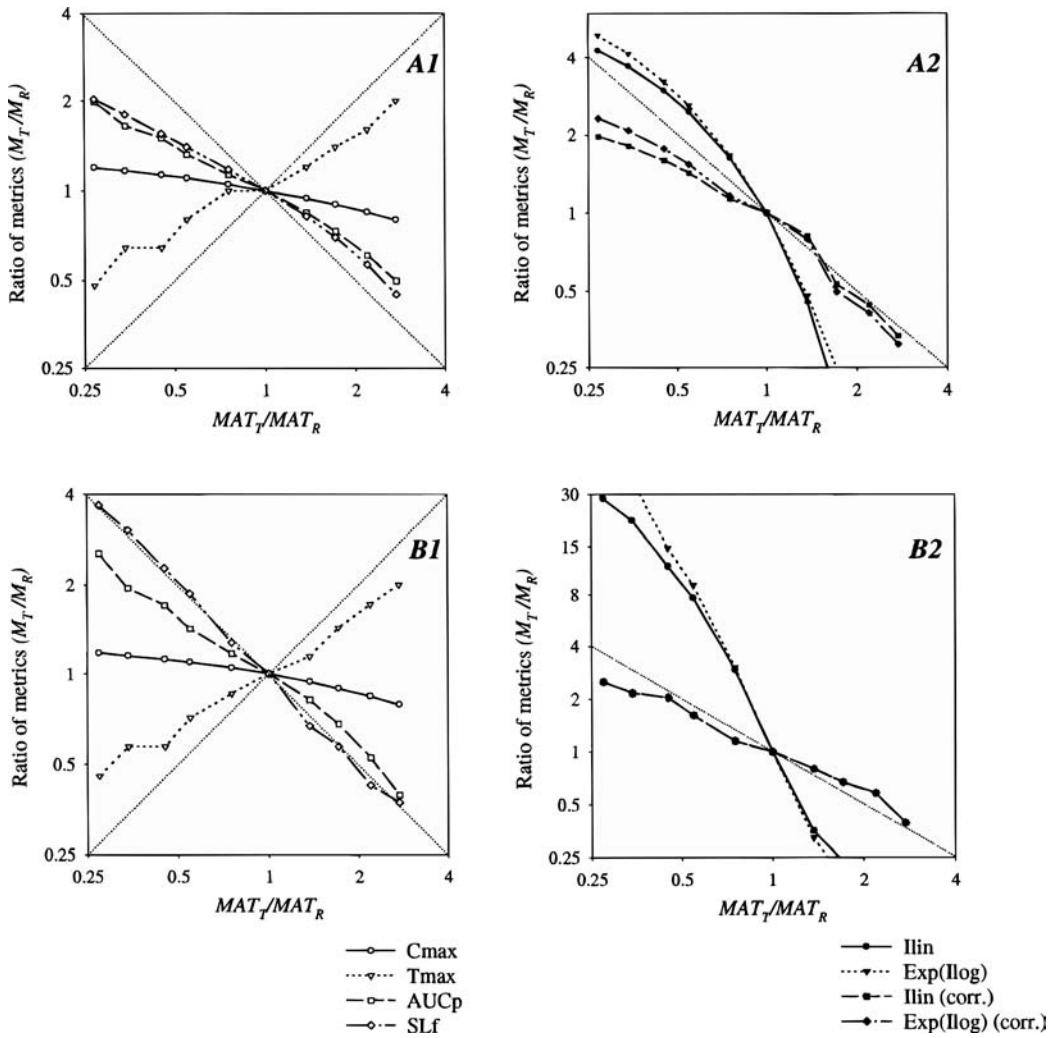

Fig. 3. The effect of changing the ratio of the mean absorption times (and CV_A^2), for the test (MAT_T) and reference ($MAT_R = 0.73$) formulations, on ratios of indirect metrics (M_T/M_R) for C_{max}, T_{max}, AUC_p, SL_f (left), and intercept metrics (right). (A): IG model, $CV_A^2 = 1.78$; (B): IG model, $CV_A^2 = 0.63$.

RESULTS

Figure 3 shows the kinetic sensitivities of ratios of various metrics, observed between the test and reference drug products (M_T/M_R), with respect to the corresponding ratios of mean absorption times (MAT_T/MAT_R). The results are presented for two values of the shape parameter, $CV_A^2 = 1.78$ (A) and $CV_A^2 = 0.63$ (B). The dotted lines (diagonals) indicate the optimal case of complete sensitivity. Figure 4 illustrates the kinetic sensitivities of the ratios of various metrics, recorded between the test and reference formulations (M_T/M_R), with respect to the corresponding ratios of the shape parameter ($CV_{A,T}^2/CV_{A,R}^2$). The kinetic sensitivities of the various metrics are summarized in Table I which presents the slopes of the sensitivity curves at the center of the graph when the two formulations have identical properties ($M_T/M_R = 1$).

DISCUSSION

Kinetic sensitivities of various metrics were evaluated in this study particularly for the IG model. This model was found, in earlier investigations, to characterize pharmacokinetic observations satisfactorily and more flexibly than the EX model (10,11). Therefore, it was interesting to explore, with the IG model, the properties of measures applied for the comparison of early concentration-time profiles, and of early exposure, in bioequivalence studies which were analyzed earlier with the EX model (8).

The performances of the metrics shown in Figs. 1A and 1B, obtained by using the more realistic IG model, are in accordance with the properties found for the EX model previously (8): SL_f exhibits high sensitivity and C_{max} low sensitivity. The sensitivity of SL_f is dependent on the shape parameter of the absorption profile, CV_A^2. T_{max} and partial *AUC* are moderately sensitive with both kinetic models. However, from a practical point of view the high sensitivities of T_{max} and SL_f may be counterbalanced by their unfavorable statistical properties (2,19). Procedures for a more appropriate analysis of T_{max} have been proposed (20). Again, table I demonstrates the low sensitivities of C_{max} with both models. T_{max} and partial *AUC* are moderately sensitive. The feathered slope (SL_f) method has generally high sensitivity.

While the EX model predicts full sensitivity for the intercept metrics (3,8), they show supersensitivity for the more realistic IG absorption model without an adjustment for lag time (Fig. 3A2). At first, this magnifying effect would seem to be attractive. However, the apparent supersensitivity does not, in fact, reflect changes in the MAT ratio but indicates an extraneous factor, the omission of a lag time in the model. Full kinetic sensitivity is restored when a correction is made for the apparent lag time (Fig. 3B2). Table I also illustrates the intercept metric is supersensitive when it is applied blindly with the IG model. However, if a reasonably T_{lag} is used with the IG model then generally high sensitivity is obtained.

All metrics shown in Fig. 4C1 (C_{max}, T_{max}, partial *AUC*, and feathered slope) fail to reflect differences between the shapes of the concentration-time profiles of the test and reference formulations, i.e. between the dispersions of absorption times. This implies that even such changes as shown in the simulations (Fig. 2B) cannot be detected by these metrics. The intercept metrics, however, show a satisfactory sensitivity to the $CV_{A,T}^2/CV_{A,R}^2$ ratios when these are higher than approximately 0.7 and, after lag time correction, also for lower values (Fig. 4C2). These results are also reflected by the slopes of the sensitivity curves at the center of the graph (Table I). Ratios of C_{max}, T_{max}, partial *AUC*, and feathered slope are seen again to be almost completely insensitive to the ratios of the shape parameters. In contrast, the intercept metric exhibits supersensitivity, both with and without correction for lag time. However, Fig. 4B indicates that, for the metrics corrected for lag time, the largest value of the slope is actually observed when $M_T/M_R = 1$. The overall impression over a range of M_T/M_R is still, after a correction for a lag time, the intercept metric has nearly full sensitivity to the shape factor.

Since the IG model also accounts for the $C(t)$ profiles with

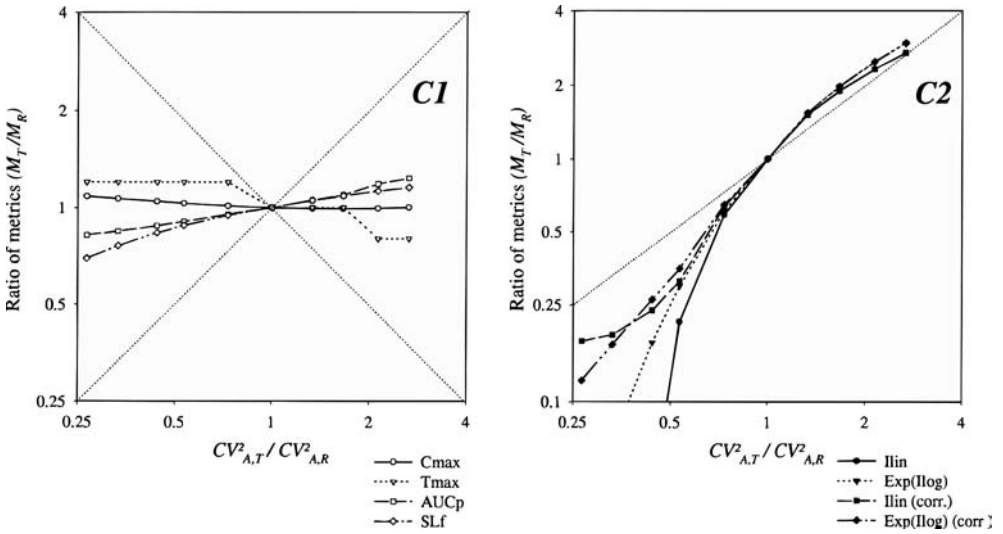

Fig. 4. The effect of changing the ratio of the relative dispersion times (CV_A^2), for the test ($CV_{A,T}^2$) and reference ($CV_{A,R}^2 = 1.88$) formulations, on ratios of indirect metrics (M_T/M_R) for C_{max}, T_{max}, AUC_p, SL_f (C1), and the intercept metrics (C2). $MAT = 0.73$ was assumed.

Table I. Sensitivity of the Bioequivalence Metrics Calculated as Slopes of the Curves in Figs. 3 and 4 at the Centre of the Graph

	C_{max}	T_{max}	AUC_p	SL_f	I_{lin}	I_{log}	I_{lin} (corr.)[a]	I_{log} (corr.)[a]
IG − MAT[b]	−0.18	0.45	−0.51	−0.61	−2.2	−2.1	−0.80	−0.91
IG − MAT[c]	−0.18	0.58	−0.63	−1.1	−3.2	−3.5	−0.74	−0.77
IG − CV_A^2	−0.03	−0.19	0.17	0.19	1.9	1.7	1.6	1.5

[a] Corrected for lag time.
[b] $CV_A^2 = 1.88$.
[c] $CV_A^2 = 0.73$.

an apparent lag time (Figs. 1 and 2B), the results demonstrate the usefulness of the method of Csizmadia and Endrenyi (13) in cases where a correction for an apparent lag time is necessary. The conclusions based on the more realistic IG model for the model independent (scale) parameter MAT ($= 1/k_a$) generalize previous results which were obtained for the simple first-order absorption model.

The present study shows, however, that the influence of the absorption profile on the resulting plasma concentration-time curve is insufficiently described by only one parameter (MAT); at least one additional parameter is necessary in most cases to quantify the profile of absorption rates. Thus, a single empirical metric cannot account for all characteristics of the absorption process. Nevertheless, a metric may be sensitive to changes in both the scale and shape parameters, MAT and CV_A^2. To illustrate this with a real-life example, Fig. 5 shows the mean concentration-time curve observed in healthy volunteers after the administration of a morphine sustained-release tablet, characterized by $MAT = 3.3$ h and $CV_A^2 = 1.1$ (11). This is considered to play the role of the reference product which is compared with curves simulated for two test products with $CV_A^2 = 0.28$ and 4.4, respectively (leaving AUC and MAT unchanged) (Fig. 5). Although both bioavailability (i.e., AUC) and MAT remained constant, the profiles can be hardly called "equivalent", as it would appear from indirect metrics which would be only sensitive to changes in AUC and/or MAT. Since the intercept metrics are sensitive to both CV_A^2 and MAT changes, one would detect the changes shown in Fig. 5, however, without the ability of an causal interpretation. The joint effect of MAT and CV_A^2 on the properties of empirical metrics will have to be explored. Note, that in contrast to MAT where the total mean residence time has been proposed as a more direct measure in bioequivalence tests (21), moment analysis cannot be similarly applied to an indirect CV_A^2 estimation since the relative dispersions of the absorption and disposition process are not additive.

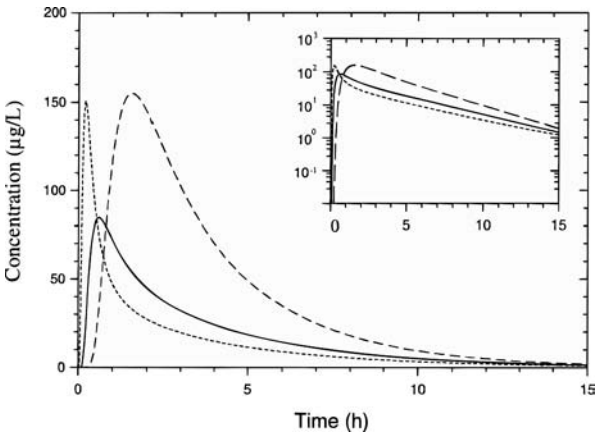

Fig. 5. The plasma concentration-time curve after oral administration of 90 mg morphine sustained-release tablet (solid line) predicted using the average absorption parameters (F = 0.35, $MAT = 3.3$ h, $CV_A^2 = 1.1$) together with the average parameters of the biexponential disposition process after iv administration (11). Curves simulated for $CV_A^2 = 4.4$ (short dashed line) and $CV_A^2 = 0.28$ (long dashed line) are shown for comparison.

A limitation of the present study (and all earlier analogous papers based on the EX model) is the assumption of a specific disposition model; the effects of absorption parameters were studied keeping the elimination constant fixed.

The determination of kinetic sensitivities is only the first step in evaluating the performances of metrics which are sensitive to changes in the shape parameter CV_A^2. An appropriate statistical analysis accounting for observational errors and the effects of intra- and interindividual variability of model parameters should be the next step. While performances of AUC and MAT -related measures with regard to data errors and parameter variations were tested using the EX model (2,3) such an evaluation is also necessary for CV_A^2 sensitive measures. These effects will be discussed in a future publication. However, recent studies suggest the kinetic sensitivities of metrics have substantially larger effects on the features of tests for bioequivalence than the random variations of measurements and parameters (7,8). Thus, while the IG model is useful for the estimation of absorption parameters in bioavailability studies (10,11), it may also prove a promising tool for the development and testing of bioequivalence metrics.

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