Bioequivalence metrics for absorption rates: linearity, specificity, sensitivity

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Abstract
Aims*: In order to ensure the therapeutic equivalence of generic products, it would be important to contrast measures additional to Cmax in order to assess differences in absorption rates. Our aim was to compare partial AUC (PAUC), Swing, and PTF to Cmax in terms of sensitivity, specificity and linearity under identical kinetic conditions.*
Methods*: Single-dose and multiple-dose concentration curves were generated assuming one-compartment models. Kinetic sensitivity curves were obtained by gradually changing the absorption rate constant and keeping all other parameters fixed.*
Results*: Ideally, a metric should reflect specifically the investigated kinetic feature (e.g., the rate of absorption), be linearly related to it, and should exhibit high kinetic sensitivity. Cmax is related nonlinearly to the rate of absorption, is nonspecific to it (reflects also the extent of absorption as well as the rates of disposition processes), lacks kinetic sensitivity even following a single administration. Compared to Cmax, PAUC was always more sensitive under every investigated condition. Swing and PTF showed high kinetic sensitivity but, in contrast to PAUC, they could be evaluated only in multiple-dose studies.*
Conclusion*: Under identical conditions, different metrics provide widely differing point estimates. Differences in kinetic sensitivity among bioequivalence metrics should be accounted for when results of different metrics are compared.*

Keywords: *Bioequivalence, Generic drugs, Partial AUC, Pharmacokinetics*

Introduction

There is general consensus on the criteria for evaluating the equivalence of the extent of absorption in two drug products which exhibit simple linear kinetics, following their single administration to individuals [1]. In contrast, there is no agreement on testing parameters for absorption rates. Major regulatory agencies apply different criteria. For example, the US Food and Drug Administration has identical expectations for judging the equivalence of two Cmax values (maximum plasma concentration) and two AUC values (area under the curve contrasting plasma concentration with time). The European Community considers that Cmax has generally larger variability than AUC and allows a more relaxed criterion to the former. The Canadian Health Protection Branch requires, in view of the prevailing uncertainty about the variability of Cmax, that only the ratio of AUC values, recorded for the two formulations, should be between preset limits [2-5].

A source of uncertainties is that Cmax is only an indirect measure of absorption rates and absorption rate constants, as are other indices. Thus, these metrics may have limited specificity, sensitivity and precision. Explorations have been conducted for an appropriate metric testing the equivalence of absorption rates. For example, Endrenyi et al. [6,7] suggested that Cmax/AUC should be used as an indirect index of absorption rates and proposed regulatory criteria based on the computed variability of Cmax/AUC and Cmax. Bois et al. [8] and Reppas et al. [9] compared several indices under various modeling assumptions but have not reached decisive conclusions. Studies of the effective evaluation of bioequivalence have considered mostly the single administration of drugs which follow uncomplicated linear kinetics. Information on the quantitative features of procedures and in-

dices for testing bioequivalence in the steady state is more limited.

Therefore, the present communication has two main goals: (1) To develop principles by which metrics characterizing pharmacokinetic features, especially those involving bioavailability and bioequivalence, can be evaluated; (2) to illustrate the application of the principles following single and repeated dose administration.

Useful Features of Metrics Characterizing Bioavailahility and Bioequivalence

Studies were performed [8-10] which recorded difficulties and complications in evaluating indirect metrics which characterize absorption rates, and evaluated their comparisons. Therefore, criteria for assessing features of such metrics will be discussed.

An ideal metric used for the evaluation of bioavailability and bioequivalence should reflect specifically the underlying kinetic parameter, be related linearly to it, have high kinetic sensitivity, and exhibit high statistical insensitivity. Direct metrics possess these features; the performance of AUC reflecting the extent of drug absorption serves as an example. Cmax is an indirect metric for the rate of absorption; its general characteristics and some of the difficulties noted after the single administration of drug products will be illustrated in this section.

Specificity

A good metric should represent solely, specifically the investigated kinetic feature. For example, AUC is specific since it reflects only, in conjunction, plasma clearance and the extent of absorption; it does not depend on other kinetic parameters. In contrast, Cmax reflects nonspecifically the rate of absorption; it depends also on the rates of disposition processes as well as the extent of absorption. Cmax/AUC is more specific than Cmax since it does not reflect the extent of absorption [6]. However, this parameter still varies along with the rates of disposition processes.

Linearity

The relationship between the applied metric and the investigated kinetic feature is characterized by a mathematical relationship. In the simplest case, the relationship is linear. For example, the measured AUC depends linearly on the extent of absorption. On the other hand, AUC is related reciprocally to plasma clearance. Consequently, the logarithm of AUC is connected linearly to the logarithms of both the extent of absorption and plasma clearance.

In contrast, Cmax is related nonlinearly to ka (the absorption rate constant). As discussed in the next subsection, the lack of kinetic sensitivity is a consequence of nonlinearity. Moreover, the observed variation of nonlinear metrics depends not only on the intraindividual but also intersubject variability of the underlying parameter(s). In addition, criteria for corresponding, parallel regulatory conditions depend on the levels of the sources of variation.

Kinetic Sensitivity

If a change in an investigated kinetic parameter elicits an identical change in the measured metric, then the latter can be said to exhibit full kinetic sensitivity. Full kinetic sensitivity prevails with respect to the extent of absorption: a 25% change in the latter elicits a 25% change in AUC. If, however, a change in the parameter gives rise to a much smaller change in the metric then, the metric lacks full kinetic sensitivity to the parameter.

Kinetic sensitivity can be evaluated, approximately, from the slopes of relationships between the metrics and the investigated parameters. Use of a double-logarithmic relationship is convenient since both kinetic metrics and parameters have multiplicative character.

However, studies of the effective evaluation of bioequivalence have usually considered single-dose administration scenarios for drugs with uncomplicated linear kinetics. There are substantially fewer studies in the steady state. Even though it is generally recognized that Cmax is an insensitive metric [6-9] much less is known about its behavior at steady state, and how Cmax sensitivity compares to other steady-state metrics proposed in the literature. Furthermore, results obtained from single-dose studies cannot be directly compared with the steady-state results unless the kinetic conditions are identical. Partial AUC (PAUC) is a recently introduced early exposure measure defined as the area under the curve until the time of maximum concentration (Tmax) of the reference formulation [10]. Its kinetic properties have been investigated following single-dose administration but not under steady-state conditions.

Therefore, we set the goal to compare the kinetic sensitivities of Cmax and the proposed alternative metrics, including PAUC, following single and repeated dose administrations under identical conditions.

Methods

The kinetic model in the calculations and simulations assumed single exponential terms for absorption and disposition. Consequently, the time (t) course of concentrations (C) was described by the expression following single administration:

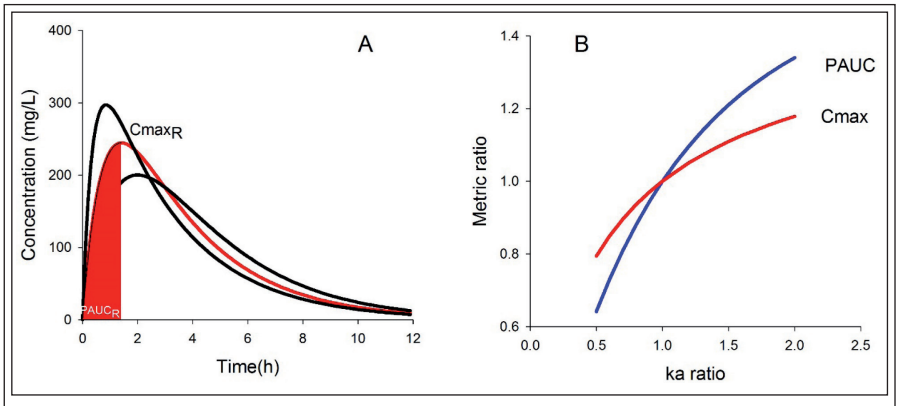

Figure 1 *Metric definitions and metric sensitivity following a single oral dose. (A) Concentration-time profiles of the Reference (R) product in red and two Test (T) formulations, in black, following a single dose. Absorption rate constants are compared indirectly, by comparing numerical characteristics called bioequivalence metrics from the observed concentrations. The left panel of the figure illustrates the two regulatorily accepted bioequivalence metrics for absorption rates: Cmax and PAUC (shaded area). The bioequivalence decision is based on the statistical comparison of the appropriate metrics such as $Cmax_T$ versus $Cmax_R$. (B) Calculated kinetic sensitivity curves contrasting the metric ratio with the corresponding ka, absorption rate constant, ratios.*

$$C(t) = \frac{F * Dose}{Vd} \frac{ka}{ka - \frac{Cl}{Vd}} \left(e^{-\frac{Cl}{Vd}t} - e^{-ka*t} \right) \quad [1]$$

and at steady state:

$$C(t) = \frac{F * Dose}{Vd} \frac{ka}{ka - \frac{Cl}{Vd}} \left(\frac{e^{-\frac{Cl}{Vd}t}}{1 - e^{-\frac{Cl}{Vd}T}} - \frac{e^{-ka*t}}{1 - e^{-ka*T}} \right) \quad [2]$$

where F is the fraction of dose absorbed into the systemic circulation, Vd is the apparent volume of distribution, T is the maintenance time interval, Cl is the drug clearance and ka is the absorption rate constant. The condition of single drug administration is approached as T is increased.

The application of several metrics has been proposed [9] for repeated administration bioequivalence studies. They include the maximum and minimum concentration (Cmax and Cmin), and the peak-trough fluctuation (PTF) and Swing which are defined as:

PTF = Cmax/Cmin

Swing = (Cmax - Cmin)/Cmin

where Cmax and Cmin are the maximum and minimum concentrations, respectively, during a dosing interval.

The true average parameters for the reference product, drug R, were arbitrarily set to ka = 1.39h^{-1}, Vd = 1 L, Cl = 0.347 L/h, Dose = 400 (in arbitrary units).

The kinetic equations were evaluated using Matlab (ver 2017b, MathWorks, USA).

Results

Single-Dose Administration

Figure 1A shows concentration profiles of a reference (R) and a test (T) drug product which differ in their rate constants but not in their extents of absorption. For the quantitative comparison of the curves appropriate single-number characteristics are needed. These are called bioequivalence metrics. Figure 1A illustrates the definitions of two commonly used metrics, Cmax and PAUC. The figure shows in red the concentration profile for the reference product with the stated kinetic parame-

Table I *Sensitivity of absorption metrics following a single dose administration. The sensitivity of a bioequivalence metric is defined as the slope of the curve contrasting logarithmic absorption rate constants and logarithmic metric ratios. Sensitivities were calculated in two different kinetic conditions, when the elimination rate is relative fast to that of absorption (ka/ke=4) and when it much slower (ka/ke = 12)*

Metrics	Sensitivity	
	ka/ke ratio = 4	ka/ke ratio = 16
Cmax	0.269	0.123
PAUC	0.498	0.358

ters. The concentration of two simulated subjects are also shown in black whose absorption rate constants are different from that of the reference formulation but who have the same extent of absorption, and therefore the same AUC.

As the absorption rate constant of the test formulation gradually increases (or decreases) relative to the reference product so do the corresponding metrics. The quantitative relationships between absorption rate constants and the metrics with default kinetic parameters are displayed in Figure 1B. The slope between the logarithmic metric and ka ratios can be used for numerical comparison. Slopes approximating 1.0 suggest satisfactory, high sensitivity while small values indicate low sensitivities. Table I shows that the slopes of Cmax and PAUC are below 1. Therefore, compared to AUC, Cmax is not a sensitive metric. Compared to Cmax, PAUC is a more sensitive measure. However, neither indirect metric is specific, the slopes depend on the ka/ke ratio (Table I).

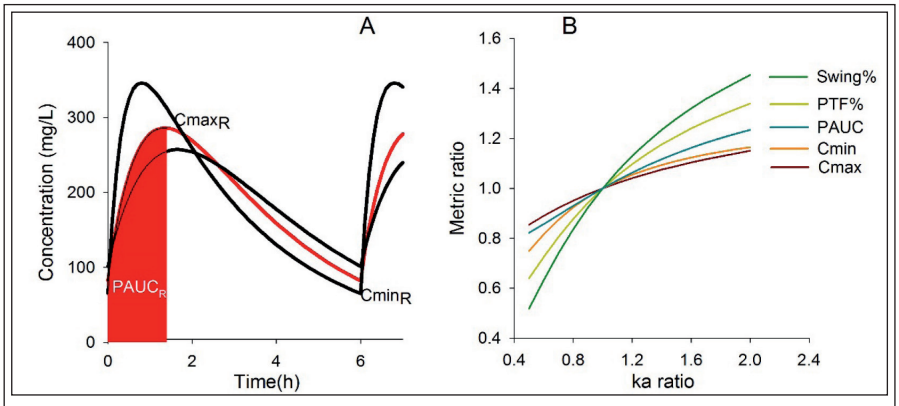

Figure 2 *Metric definitions and metric sensitivity following repeated dosing. (A) Concentration-time profiles of the Reference (R) and two Test (T) formulations in steady state. The left panel shows three directly calculated metrics for the reference drugs: the maximum concentration ($Cmax_R$): the minimum concentration ($Cmin_R$), and the area until Tmax ($PAUC_R$). (B) Calculated kinetic sensitivity curves contrasting the metric ratio with the corresponding ka, absorption rate constant ratios. PTF and Swing are two additional, derived metrics defined as Cmax/Cmin and (Cmax-Cmin)/Cmin, respectively.*

Repeated Drug Administration

The kinetic parameters in Figure 2A are the same as in Figure 1A but now the concentration profiles represent the steady-state condition. Cmax and PAUC increase with rising absorption rate constant, relative to the reference product, while Cmin (the concentration just before the next dose) decreases. Therefore, for easy visual comparison for Cmin we computed the $Cmin_R/Cmin_T$ ratio instead of $Cmin_T/Cmin_R$. Figure 2B shows that, at steady state, Swing is the most sensitive parameter followed by PTF and PAUC. Compared to these metrics, Cmax and Cmin are much less sensitive (Table II). Just as in the case of single dose administration, all slopes are smaller than 1 and they decrease in parallel with ka/ke ratio. The slopes are higher in Table I than in the corresponding entries of Table II.

Table II *Pharmacokinetic sensitivities of 5 metrics estimating absorption rates in the steady state. Under both kinetic conditions the between dose interval (T) equals with the drug half-life.*

Metrics	Sensitivity	
	ka/ke ratio = 4	ka/ke ratio = 16
Cmax	0.213	0.079
Cmin	0.287	0.062
PTF	0.499	0.138
Swing	0.673	0.360
PAUC	0.307	0.122

Discussion

We computed and compared kinetic sensitivities of absorption metrics following single and repeated dosing in two different kinetic conditions. Even though the numerical details were different, the relative ranking remained the same. PAUC was always more sensitive than Cmax and metrics estimated from single dose studies were more sensitive than their steady-state counterparts. However, considerations for assessing comparative absorption rates are much more difficult and complicated in the steady state than following the single administration of drugs. The decrease in sensitivity was expected since the estimations generally involve the determination of the maximum concentration or a quantity related to it. The net height of concentration peaks (the fluctuation of concentrations) is lower in steady state than following a single administration and they further decrease with increasing accumulation. Nevertheless, Swing and PTF at steady state were more sensitive than the metrics applied following a single dose. Therefore, it is possible construct sensitive metrics that can be applied under steady-state

conditions. This is important because in certain cases bioequivalence should be demonstrated in the steady state possibly because single-dose studies cannot be performed at all. Additional multiple-dose bioequivalence studies are needed for prolonged-release formulations [11]. Multiple-dose bioequivalence studies are also accepted if a single-dose study cannot be conducted in healthy volunteers due to tolerability reasons. Multiple-dose bioequivalence studies are recommended with drugs with dose- and time-dependent kinetics such as strong enzyme inductors. In the latter case, the sensitivity can be even higher at steady state compared to a single dosing [12]. The reason is that due the enhanced elimination rate the ka/ke ratio is smaller and, as we showed, the kinetic sensitivity of the absorption metrics negatively correlates with the ka/ke ratio (Tables I and II).

Conclusion

Under identical conditions different metrics provide differing point estimates. Differences in kinetic sensitivities among bioequivalence metrics should be accounted for when results of different metrics are compared. The kinetic analysis of bioequivalence metrics helps also not only to design new, sensitive metrics but also to identify clinical situations when the results of standard single-dose bioequivalence studies cannot be easily extrapolated to clinical settings.

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