Pharm Res (2011) 28:1939–1947
DOI 10.1007/s11095-011-0421-x

EXPERT REVIEW

Using Partial Area for Evaluation of Bioavailability and Bioequivalence

Mei-Ling Chen • Barbara Davit • Robert Lionberger • Zakaria Wahba • Hae-Young Ahn • Lawrence X. Yu

Received: 5 November 2010 / Accepted: 4 March 2011 / Published online: 13 April 2011

ABSTRACT Assessment of bioavailability/bioequivalence generally relies on the comparison of rate and extent of drug absorption between products. Rate of absorption is commonly expressed by peak concentration (C_{max}) and time to peak concentration (T_{max}), although these parameters are indirect measures of absorption rate. Recognizing the importance of systemic exposure to drug efficacy and safety, FDA recommended that systemic exposure be better used for bioavailability/bioequivalence assessment. Apart from peak exposure and total exposure, FDA also recommended a new metric for early exposure that is considered necessary when a control of input rate is critical to ascertain drug efficacy and/or safety profile. The early exposure can be measured by truncating the area under the curve at T_{max} of the reference product ($PAUC_{r,tmax}$) or some designated early time after dosing. The choice of truncation is most appropriately based on PK/PD relationship or efficacy/safety data for the drug under examination. Compared with C_{max}, $PAUC_{r,tmax}$ has higher sensitivity in detecting formulation differences and may be more variable. If the metric is highly variable, the reference-scaling approach can be employed for bioequivalence evaluation. The partial area metric is useful in PK/PD characterization as well as in the evaluation of bioavailability, bioequivalence and/or comparability.

KEY WORDS bioavailability/bioequivalence · early exposure · partial area · partial AUC · truncated area

M.-L. Chen (✉)
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration (FDA)
10903 New Hampshire Avenue, Building 51, Rm. 4108
Silver Spring, Maryland 20993–0002, USA
e-mail: meiling.chen@fda.hhs.gov

B. Davit · R. Lionberger · Z. Wahba · L. X. Yu
Office of Generic Drugs, Office of Pharmaceutical Science
Center for Drug Evaluation and Research, FDA
Rockville, Maryland, USA

H.-Y. Ahn
Office of Clinical Pharmacology, Office of Translational Sciences
Center for Drug Evaluation and Research, FDA
Silver Spring, Maryland, USA

INTRODUCTION

Regulatory assessment of bioavailability and bioequivalence has relied on the comparison of rate and extent of drug absorption between products (1,2). For systemically acting drugs, this is generally achieved by measuring drug concentrations in an accessible biological fluid, such as plasma or serum, over the time course of a pharmacokinetic study in humans. Derived from the plasma or serum concentration-time profile, the rate of absorption is commonly expressed by C_{max} and T_{max}, whereas the extent of absorption is expressed by the area-under-the-curve to the last quantifiable drug concentration (AUC_t) and/or to time infinity (AUC_∞). To establish bioequivalence, the 90% confidence interval of the geometric mean ratio of the test to reference product has to meet the 80–125% limit for all the aforementioned pharmacokinetic parameters except T_{max} (3) that should be similar for the test and reference product. Statistical comparison is not performed for T_{max} due to the lack of appropriate methods (4).

Strictly speaking, C_{max} and T_{max} are indirect measures for rate of absorption, as 'rate' is defined by a rate constant (ka) or rate profile (5). Direct measures such as rate constant or rate profile are not used for bioequivalence evaluation

for a number of reasons (5). Model-based rate constants are predicated on assumptions about the absorptive process, and the absorption course of a drug is usually more complex than a simple first-order or zero-order process. Drug release and absorption *in vivo* is further implicated in the presence of variable gastrointestinal environment of human subjects and different types of dosage forms/formulations (*e.g.*, immediate-release or extended-release) used in the study. Even without these problems, estimating absorption rate constant values for bioavailability and bioequivalence studies would still be difficult because of high variability. While numerical deconvolution methods may provide rate profiles that reflect rate of absorption, these methods require plasma concentration-time curves from both intravenous and oral administration of a drug to the same individuals. Further, a drawback of using rate profiles for bioequivalence evaluation is that there is no appropriate statistical method to allow comparison of these profiles.

In 2000, recognizing the fact that systemic exposure is the key for drug safety and efficacy, and the challenges inherent in identifying a suitable pharmacokinetic measure to express both rate and exposure, FDA recommended a change in focus from the measures of absorption rate to measures of systemic exposure in bioavailability and bioequivalence studies (3). Defined relative to the total, peak and early portions of the plasma/serum profile, systemic exposure can be expressed as total exposure, peak exposure, and early exposure, respectively (6). According to the FDA's Guidance to Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations (BA/BE Guidance), the total exposure to a drug is readily expressed by AUC_∞ (or AUC_t) and peak exposure by C_{max} (3). Hence, both AUC and C_{max} are used as measures for bioavailability and bioequivalence, more in terms of their capacity to assess peak exposure and total exposure than their capacity to reflect rate and extent of absorption (3,5). The BA/BE Guidance further indicates that an assessment of early exposure may be appropriate for some immediate-release products where a better control of drug input rate is important for therapy (3). In general, for bioequivalence comparisons of such immediate-release drug products, the BA/BE Guidance recommends determining early exposure by calculating partial AUC until the population median T_{max} of the reference product observed in the study. Because of the high variability in measurement of partial AUC, the BA/BE Guidance also recommends that at least two quantifiable samples be collected before the expected peak time to allow adequate estimation of the partial area. Early exposure can also be estimated by truncating the AUC at any early time after drug administration, depending on the pharmacokinetic/pharmacodynamic (PK/PD) relationship of the drug product under examination. To make a fair comparison, an earlier study showed that the cutoff for partial AUC should be at the same time for both test and reference within each individual (7). Additionally, this study showed that equivalence determination relies highly on the cutoff point chosen unless both products have similar absorption rate throughout the entire absorption phase. In general, when cutoff time $>T_{max}$, the farther the cutoff point from T_{max}, the tighter the confidence interval becomes.

The aims of this article are to (a) provide an overview on the characteristics of partial AUC (PAUC) metrics for the assessment of systemic exposure in bioavailability and bioequivalence studies, and (b) use actual data to illustrate the potential application of PAUC metrics in clinical pharmacology and biopharmaceutics.

SENSITIVITY OF PAUC WITH AN EARLY CUTOFF

Considerable efforts have been undertaken to study the use of partial AUC as a measure of early exposure in bioavailability and bioequivalence studies (7–13). Partial AUCs calculated up to reference T_{max} ($PAUC_{r,tmax}$) were generally found to be more sensitive than C_{max} in detecting absorption rate differences between formulations (7,9,12–14). There may be alternative metrics that are as sensitive or more sensitive than $PAUC_{r,tmax}$ for the assessment of absorption rate in bioequivalence studies (15,16). However, as discussed in the previous section, in view of the significance between drug exposure and efficacy/safety profile, $PAUC_{r,tmax}$ is chosen to express both input rate and early exposure in the regulatory setting. In this context, it is important to have a better understanding of the sensitivity of $PAUC_{r,tmax}$ in detecting rate differences between products.

Pharmacokinetic simulations have previously been utilized to study the behavior of C_{max} and $PAUC_{r,tmax}$ as a function of relative changes in absorption (ka) and elimination rate (ke), using the gold standard of rate constants (14). Limitations in the model-based simulations are noted for the previous study in view of the fact that (a) only one-compartment model with first-order absorption and elimination was used, (b) perfect sampling schedule was assumed, and (c) variability was not incorporated in the model. In addition, the true sensitivity of partial AUC to detect bioequivalence differences depends not only on the underlying absorption differences between formulations, but also sources of PK variability, sampling schedule and sample size. However, with the simple simulation scheme, this earlier study illustrated that for a reference product that releases drug rapidly (ka/ke = 50), a test product with a 5-fold lower ka would still be considered bioequivalent for C_{max} (14). In contrast, none of the $PAUC_{r,tmax}$ metric met the 80–125% limits across the range of ka/ke used in the

simulation (0.02–50), indicating that $PAUC_{r,tmax}$ is more sensitive than C_{max}. The simulations also showed that the sensitivity of partial AUC decreased markedly if truncated at 1.5 and 2 times of T_{max}. This result appears to agree with the earlier finding that when the cutoff of partial AUC was greater than T_{max}, the width of the 90% confidence interval for the partial AUC metric became narrower as the cutoff time increased from T_{max} (7).

The previous study only examined the sensitivity of various metrics under the conditions where the test product released the drug slower than the reference product (T/R ratio of ka ranging from 0.1 to 1) (14). To characterize the complete picture, we expanded the simulations to include scenarios where the test product has a faster rate of absorption than the reference product. Sensitivity of a metric may be defined by the linear relationship between the T/R ratio of ka and that of the metric under examination. Figure 1 shows the relationship between C_{max} and ka (both in terms of T/R ratio) as a function of ka/ke. Using log-scale for both X and Y axes, the T/R ratio of C_{max} increases almost in a linear fashion with that of ka when ka/ke = 0.05, which is reflective of flip-flop kinetics (ka/ke < 1). However, as ka/ke increases, deviation from this linear relationship occurs, particularly when the classical kinetics (ka/ke > 1) starts operating. The greater the ratio of ka/ke (*i.e.*, the faster the absorption rate compared with elimination rate), the more deviation from the linear relationship between C_{max} and ka, indicating the lesser sensitivity of C_{max} in detecting rate differences between the test and reference products.

Figure 2 shows the relationship between T/R ratio of $PAUC_{r,tmax}$ and ka, as a function of ka/ke. A comparison of Figs. 1 and 2 revealed that $PAUC_{r,tmax}$ and C_{max} share the similar relationship with ka. However, $PAUC_{r,tmax}$ may be more sensitive than C_{max} to detect differences in ka,

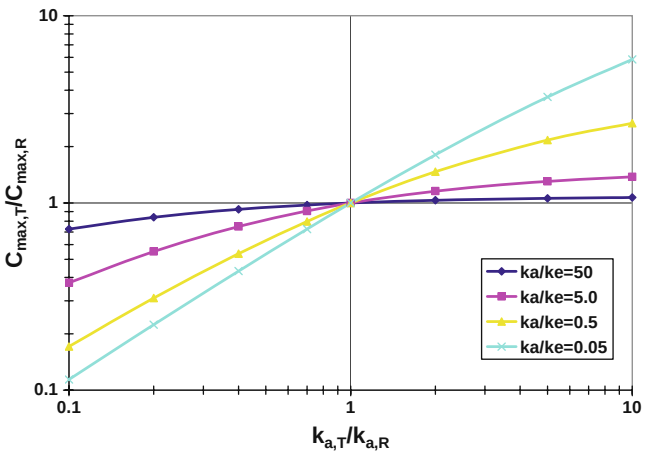

Fig. 1 Relationship of peak concentration (C_{max}) and absorption rate constant (ka) between a test (T) and reference (R) product, as a function of various ratios of ka and elimination rate constant (ke).

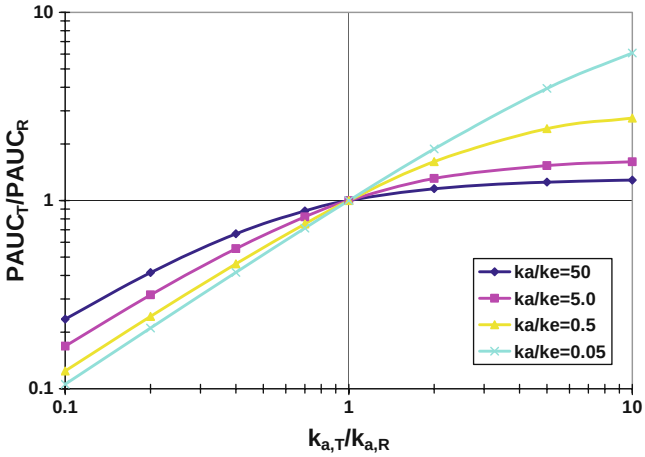

Fig. 2 Relationship of partial area to reference peak time ($PAUC_{r,tmax}$) and ka between the T and R product, as a function of various ratios of ka and ke.

especially when the test product is absorbed slower than the reference product ($ka_{,T} < ka_{,R}$). The difference in sensitivity between the two metrics is much smaller when $ka_{,T} > ka_{,R}$, which might disappear if the variability was added to the model. As shown in Fig. 2, also on log-log scale, linearity seems to prevail between $PAUC_{r,tmax}$ and ka (in terms of their T/R ratio) when ka/ke = 0.05, again, under flip-flop conditions. Deviations from this linearity arise as ka/ke ratio increases, *i.e.*, when going into classical kinetics (ka/ke > 1). The deviation becomes more pronounced when the test product is absorbed faster than the reference (*i.e.*, $k_{a,T}/k_{a,R} > 1$) as opposed to the reverse when the test product has a slower absorption rate (*i.e.*, $k_{a,T}/k_{a,R} < 1$).

It is noteworthy that the ka/ke ratio determines whether the overall pharmacokinetics of a drug is elimination rate-limited (ka/ke > 1, classical kinetics for most immediate-release products) or absorption rate-limited (ka/ke < 1, flip-flop kinetics for all extended-release products). In the former case, early exposure as expressed by $PAUC_{r,tmax}$ is primarily governed by drug absorption, while in the later case, early exposure may be equally determined by drug elimination and absorption. It appears that both C_{max} and $PAUC_{r,tmax}$ correlate better with changes in rate of absorption (ka) under flip-flop conditions for absorption rate-limited formulations, compared with classical kinetics for elimination rate-limited formulations. In this regard, it is interesting to note that an earlier study using the E_{max} model with a delay in the effect against plasma concentration also demonstrated that changes in the PD measures (such as E_{Cmax} and t_{EC50}) are reflected on the partial AUC metric only under flip-flop kinetic conditions (17). On the other hand, based on the current simulations, for more slowly absorbed test product ($ka_{,T} < ka_{,R}$), $PAUC_{r,tmax}$ is clearly more sensitive than C_{max} to detect differences in absorption rate, especially for immediate-release products that are elimination rate-limited. The advantage of sensi-

tivity in $PAUC_{r,tmax}$ over C_{max} is much smaller for absorption rate-limited formulations as found in extended-release products.

VARIABILITY OF PAUC WITH AN EARLY CUTOFF

In an effort to explore the variability of PAUCs, we calculated $PAUC_{r,tmax}$ values (to the reference T_{max} in each subject) for *in vivo* bioequivalence studies from drug applications submitted to the FDA. The database included eight studies on immediate-release products and nine studies on extended-release products. All studies were conducted in healthy subjects (N=20–36). The results are provided below with drug names blinded for proprietary reasons.

Table I summarizes the data of selected pharmacokinetic parameters from the studies with immediate-release products. All studies passed bioequivalence acceptance criteria for C_{max} and AUC_t except for three studies which did not meet bioequivalence limits for $PAUC_{r,tmax}$, including an antibiotic, antifungal and nonsteroidal anti-inflammatory drug (NSAID) III. In these studies, $PAUC_{r,tmax}$ fell outside the 80–125% limits, possibly due to the high intrasubject variability (C.V. 32–67%) and/or low T/R mean ratio (*i.e.*, point estimate, 0.68–0.95). In the case of NSAID III, the extremely low T/R ratio for the geometric mean (0.68) indicates a clear disparity in the early exposure between the two products (Fig. 3).

Table II summarizes the pharmacokinetic data of bioequivalence studies for extended-release products. All studies met the 80–125% criteria for C_{max} and AUC_t, but not for $PAUC_{r,tmax}$; two studies failed the PAUC metric including NSAID V and a calcium channel blocker. For NSAID V, the T/R geometric mean ratio of C_{max} was close to unity (0.95), yet the corresponding ratio for $PAUC_{r,tmax}$ was only 0.68. Since the intrasubject variabilities for C_{max} and $PAUC_{r,tmax}$ were similar (19 *vs.* 20% C.V.), it was clear that the early exposure differed between the test and reference product (Fig. 4). For calcium channel blocker, the high variability of $PAUC_{r,tmax}$ is likely due to the double or multiple peaks observed in many individual plasma profiles, a characteristic of these products in general. Under such circumstances, the $PAUC_{r,tmax}$ metric is not suitable, since T_{max} is ill-defined and likely not related to onset of effect.

Overall, aside from the calcium channel blocker, the intrasubject variability of $PAUC_{r,tmax}$ appeared to be lower from the extended-release products (10–25% C.V.) as opposed to immediate-release products (21–67% C.V.). A possible reason for higher variability of the immediate-release products may be the less optimal sampling schedule, particularly in the early portion of the plasma profile. The accuracy of $PAUC_{r,tmax}$ relies heavily on the frequent sampling scheme until reference T_{max}, since plasma drug concentrations decline rapidly during the absorption phase of immediate-release products. Yet, this is a *pos hoc* analysis, and the studies were neither designed to investigate the $PAUC_{r,tmax}$ metric nor powered adequately to show bioequivalence for the metric. Another explanation for the lower intrasubject variability of $PAUC_{r,tmax}$ in extended-release compared with immediate-release products may be due to the fact that early exposure (*i.e.*, $PAUC_{r,tmax}$) from immediate-release products is primarily determined by drug absorption (and its associated variability), while the early exposure to extended-release products comes from both drug absorption and elimination (and their associated variability), wherein the variability for elimination is usually less than that for absorption.

As shown in Tables I and II, in all instances where drug products passed bioequivalence on C_{max} (but not

Table I Summary Statistics of Bioequivalence Studies on Immediate-Release Products

Drug Class/Study #	Tmax Arithmetic Mean (hr)		90% Confidence Interval for T/R Ratio			Geometric Mean for T/R Ratio			Intra-Subject Variability[a] (%C.V.)		
	T	R	Cmax	AUCt	PAUCr,tmax	Cmax	AUCt	PAUCr,tmax[b]	Cmax	AUCt	PAUCr,tmax
H_2-Receptor Antagonist I	3	3	90–108	93–104	92–108	1.00	0.99	0.99	23	14	21
H_2-Receptor Antagonist II	3	3	91–108	89–103	84–102	0.99	0.96	0.92	19	16	21
β-Adrenergic Antagonist	3	3	97–117	98–108	87–110	1.06	1.03	0.98	6	12	23
Antibiotic	2	2	91–106	92–107	73–98	0.98	1.00	0.84	16	15	32
Antifungal	2	2	83–105	85–108	77–116	0.96	0.96	0.95	23	24	35
NSAID I	1	1	89–100	100–106	80–108	0.95	1.02	0.92	11	6	30
NSAID II	2	2	98–109	97–106	80–123	1.04	1.01	0.99	10	9	44
NSAID III	2	2	93–101	98–101	50–92	0.97	0.99	0.68	11	4	67

[a] Obtained from ANOVA root mean squared error (RMSE), assuming equal variability from the test and reference products

[b] Calculated to the reference T_{max} in each subject

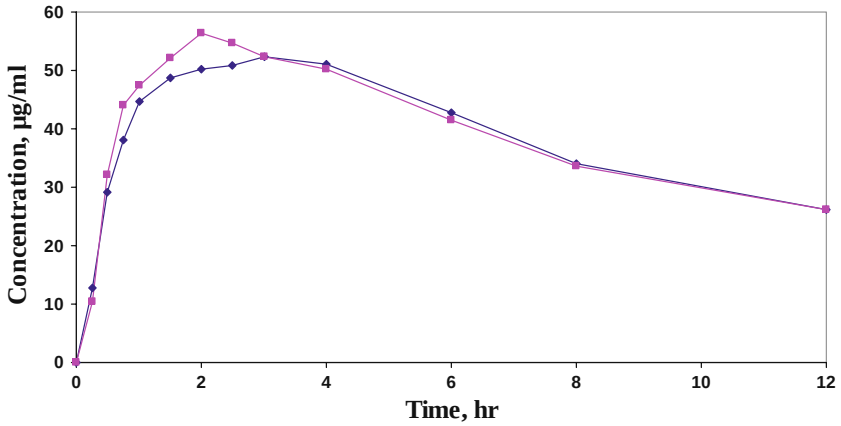

Fig. 3 The mean plasma profiles of a nonsteroidal anti-inflammatory drug (NSAID III) from two immediate-release formulations; test product (♦), reference product (■).

$PAUC_{r,tmax}$), the T/R mean ratio of $PAUC_{r,tmax}$ was less than unity, indicating a reduced absorption rate of the test product compared with the reference product. Apart from the calcium channel blocker that has multiple peaks, the failure of $PAUC_{r,tmax}$ in passing bioequivalence occurred in three (out of eight) immediate-release products, and one (out of nine) extended release product. This is in support of our simulation results that $PAUC_{r,tmax}$ is more sensitive than C_{max} to detect formulation differences in absorption rate when the test product is absorbed slower than the reference product ($ka_{,T} < ka_{,R}$), which is especially true for elimination rate-limited formulation such as immediate-release products.

An analysis of $PAUC_{r,tmax}$ from 95 bioequivalence studies on modified-release products presented at a 2010 FDA advisory committee meeting (18) indicated that the intrasubject variability of this PAUC measure decreases as the T_{max} increases (Fig. 5). Again, this is attributable to the notion that $PAUC_{r,tmax}$ derived from modified (or extended) release formulations is determined by both absorption and elimination processes, and the associated variability for absorption decreases with time. Another cause for the higher variability of $PAUC_{r,tmax}$ at shorter times may rest on the variability in gastric emptying time. This could be a significant cause of variability in $PAUC_{r,tmax}$ when T_{max} values are within the range of gastric emptying time. It should be noted that the FDA Office of Generic Drugs has recently proposed a reference-scaling approach for highly variable drugs and drug products (19–21), which can also be applied to a PAUC metric if it is highly variable (22). The reference-scaling method was not used for data

Table II Summary Statistics of Bioequivalence Studies on Extended-Release Products

Drug Class/Study #	Tmax Arithmetic Mean (hr)		90% Confidence Interval for T/R Ratio			Geometric Mean forT/R Ratio			Intra-Subject Variability[a] (%C.V.)		
	T	R	Cmax	AUCt	PAUCr, tmax	Cmax	AUCt	PAUCr, tmax[b]	Cmax	AUCt	PAUCr, tmax
Vasodilator I	5	5	87–101	85–96	83–93	0.94	0.91	0.88	15	11	14
Vasodilator II	5	4	103–116	104–116	91–100	1.09	1.12	0.95	30	17	10
Vasodilator III	5	6	90–110	90–107	90–108	0.99	0.98	0.98	19	16	17
Vasodilator IV	5	5	100–120	87–100	82–100	1.10	0.93	0.91	18	11	19
Vasodilator V	5	5	94–109	97–108	86–110	1.01	1.02	0.97	15	11	24
Analgesic	3	3	97–112	96–103	103–124	1.04	1.00	0.89	15	7	19
NSAID IV	7	6	84–98	98–106	84–103	1.02	1.02	0.95	12	9	25
NSAID V	9	5	90–101	95–104	62–75	0.95	1.00	0.68	19	9	20
Calcium- Channel Blocker	14	13	94–115	82–97	54–80	1.04	0.89	0.66	26	19	50

[a] Obtained from ANOVA root mean squared error (RMSE), assuming equal variability from the test and reference products

[b] Calculated to the reference T_{max} in each subject

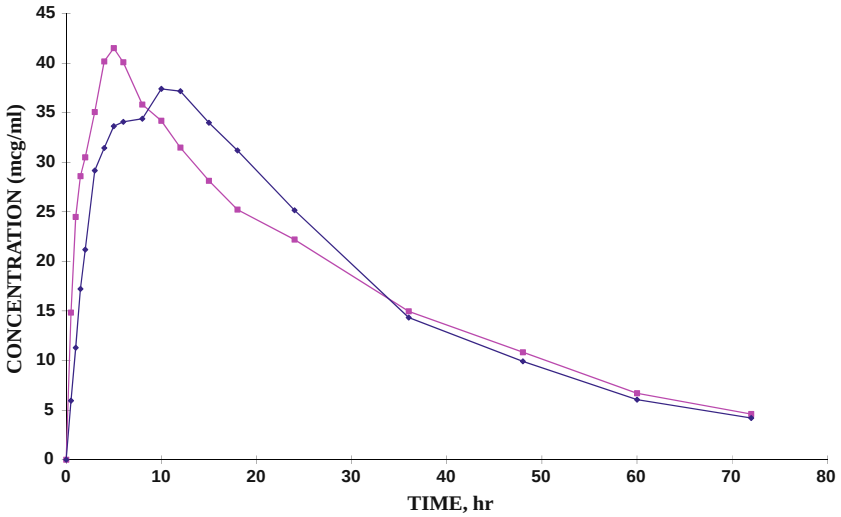

Fig. 4 The mean plasma profiles of a nonsteroidal anti-inflammatory drug (NSAID V) from two extended-release formulations; test product (♦), reference product (■).

analysis in the present paper because all the bioequivalence studies collected did not have replicated-treatment design and the intrasubject variability of reference products could not be obtained for computation.

USE OF PAUC AS EARLY EXPOSURE MEASURE

As described in the FDA's BA/BE Guidance, for immediate-release dosage forms, consideration of early exposure will be useful when a control of drug input rate (rapid or slow) is critical to achieve an optimal efficacy or safety profile (3). This is also applicable to modified-release dosage forms where a rapid onset of action is needed for drug efficacy or a slow input rate of the drug is required for safety concern. Many such modified-release products employ a multiphasic design that combines both immediate- and extended-release formulation components to achieve a quick onset of action followed by a sustained response (22).

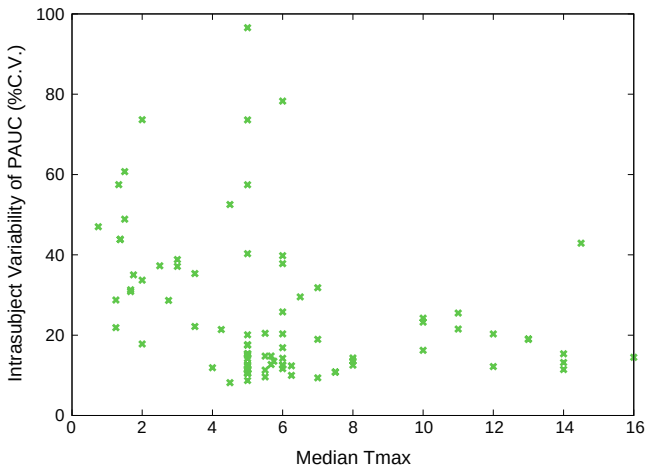

Fig. 5 Intrasubject variability in $PAUC_{r,tmax}$ as a function of median T_{max} of the reference product for 95 bioequivalence studies on modified-release products (18).

The early exposure measure such as partial area has been shown to serve as an excellent tool to characterize the PK and PD relationship (or correlation) during drug development (23). It is to be noted that the use of partial AUC as an early exposure can be truncated at reference T_{max} or at an early time other than T_{max}. For example, truncation at designated early hours post-dose may be advantageous when T_{max} cannot be identified with clarity or when the PAUC metric truncated at a specified time is more suitable for PK/PD characterization. For illustration purposes, the following section provides three case studies for which the partial area metric was used in different situations.

Case 1: Evaluation of Bioequivalence and Profile Similarity

From a regulatory standpoint, in the realm of bioequivalence evaluation, an early exposure measure is most appropriate when clinical efficacy/safety trials and/or PK/PD studies indicate the importance of better control of drug absorption into the systemic circulation (3). This is illustrated by the case of zolpidem extended-release products (22,24). The innovator product (Ambien CR®) was developed based on the results of a double-blind, placebo-controlled, ten-way crossover study where eight zolpidem formulations comprising different proportions of immediate-release and extended-release were compared with zolpidem immediate-release and placebo using PD endpoints (25). This crossover study revealed differential

effects among formulations on awakening and residual effects. A clinical trial was also conducted by the drug sponsor to confirm the efficacy and safety of the final formulation (26). In view of all the essential properties of Ambien CR®, FDA has thus suggested additional metrics (*i.e.*, $AUC_{0\text{-}1.5h}$ and $AUC_{1.5h\text{-}t}$) to ensure bioequivalence of zolpidem extended-release products (24). The $AUC_{0\text{-}1.5h}$ and $AUC_{1.5h\text{-}t}$ metrics were proposed for evaluation of zolpidem bioavailability responsible for the sleep onset and sleep maintenance phases, respectively. The choice of 1.5 h was made based on the observation that in the clinical trials about 90% of the patients were asleep at that time and that $PAUC_{0\text{-}1.5h}$ was sensitive to detect formulation differences.

Depending on the drug product and clinical indications, clinical effect may be related to the shape of the drug plasma concentration-time curve, and thus profile similarity may be desirable for assurance of bioequivalence. Under such circumstances, the use of multiple partial areas may serve the purpose for equivalence comparisons. As exemplified by the case of zolpidem extended-release tablets, the two consecutive partial AUCs, $AUC_{0\text{-}1.5h}$ and $AUC_{1.5h\text{-}t}$, replace the usual AUCt, and together with the other bioequivalence parameters (AUC_∞ and C_{max}) can ensure that the pharmacokinetic profiles of test and reference products are sufficiently similar and equivalence will be achieved in not only the early onset of effect but also the drug effects at later times (24).

Case 2: Assessment of Comparability in PK and PD

Results are from a combined PK/PD study on a hormone analog used as a hypoglycemic agent for subcutaneous injection. The original formulation (Reference, R) is derived from semi-synthetic origin, while the new formulation (Test, T) is made through recombinant DNA technology. As part of the program to assess comparability between the two formulations, an *in vivo* PK/PD study was conducted in 26 healthy volunteers where glucose levels in serum were measured as the PD response in a non-clamp study. As shown in Table III, the two formulations yielded comparable systemic exposure, including total exposure ($AUC_{0\text{-}12h}$), peak exposure (C_{max}), and early exposure ($PAUC_{r,tmax}$). All measures met the equivalence limit of 80–125%, indicating comparable PK profiles between the two formulations. Comparability in PD response (glucose concentration) was also demonstrated with all the PD measures within the range of 80–125% (Table III).

Table III Summary of Exposure and Response Measures from Two Formulations of a Hypoglycemic

Metric	90% Confidence Interval for T/R Ratio	Geometric Mean for T/R Ratio (%)
Exposure (PK) Measures		
PAUCr,tmax	86–107	96
AUC(0-12 h)	95–102	99
Cmax	85–101	93
Response (PD) Measures		
PAOCr,tmin[a]	89–125	105
AOC(0-12 h)[b]	91–124	106
Cmin[c]	96–106	101

[a] Partial area over the PD response curve from time zero to time of Cmin (*i.e.*, peak PD response)

[b] Area over the response curve from time zero to 12 h after dosing

[c] Peak PD response in terms of minimum glucose concentration in serum

Case 3: Comparison of Early Absorption

Results are from a single-dose, two-period crossover study in 24 healthy volunteers comparing a new formulation with the original formulation given orally. The drug is an anti-inflammatory agent for the treatment of rheumatoid arthritis and osteoarthritis. The original formulation (Reference, R) is an immediate-release dosage form from which the active drug substance is completely absorbed with peak plasma concentrations occurring within 2–4 h. The new formulation (Test, T) is also an immediate-release product, containing an inclusion complex of drug and cyclodextrin. It was expected that the spatial configuration of cyclodextrin would enhance the solubility and wettability of the drug, thereby leading to a faster rate of absorption. All doses were administered after an overnight fast, and volunteers continued to fast for 2 h. A close examination of individual plasma profiles showed a well-defined second peak in some subjects, suggesting the presence of enterohepatic circulation. In a few subjects, the second peak was, in fact, higher than the first peak. Hence, determination of T_{max} could not be ascertained, and the early exposure measure (PAUC) was used. Table IV gives the summary statistics of pharmacokinetic data from the study. Using the limits of 80–125%, equivalence was shown between the two formulations for total exposure (AUC_t and AUC_∞) and peak exposure (C_{max}). However, there was a marked difference in the early exposure as assessed by the partial AUC to 2 h after dosing. This might be expected as the

Table IV Summary of Exposure Measures from Two Formulations of an Anti-inflammatory Drug

Metric	90% Confidence Interval for T/R Ratio	Geometric Mean for T/R Ratio (%)
PAUC(0–2 h)	125–154	1.38
AUCt	100–111	1.05
AUCinf	100–112	1.06
Cmax	106–120	1.12

new formulation was meant to increase the absorption rate of the drug, and, indeed, plasma concentrations before 1 h were found to be consistently higher for the new formulation. Based on our simulations, when $ka,_T > ka,_R$, C_{max} may not be less sensitive than $PAUC_{r,tmax}$ to differentiate changes in absorption rate. However, the simulation results cannot apply to this case study, since the calculation of PAUC(0–2 h) was complicated by the presence of double peaks in some individuals. The difference in the early exposure to the drug was also reflected in another PK/PD study conducted in 48 patients where a faster and earlier pain relief was observed after the administration of the new formulation over the original formulation. Hence, the PAUC metric, compared with C_{max}, was proved to be a better indicator for faster drug absorption from the new formulation.

CONCLUSIONS

An assessment of early exposure may be necessary when the input rate of a drug is critical to ascertain the drug efficacy and/or safety profile. Early exposure can be defined relative to the early portion of the plasma concentration-time profile and measured up to the reference T_{max} ($PAUC_{r,tmax}$) or some other designated time after dosing. The choice of truncation for partial area is best made on the basis of PK/PD relationship or clinical efficacy/safety data for the drug under study. $PAUC_{r,tmax}$ has higher sensitivity in detecting formulation differences and may be more variable than C_{max}. If the PAUC metric is highly variable, the reference-scaling approach can be employed for bioequivalence evaluation. Application of the partial area metric has been found useful in PK/PD characterization during the drug development stage as well as in the evaluation of bioavailability, bioequivalence and/or comparability.

ACKNOWLEDGMENTS

The opinions expressed in this article are those of the authors and do not necessarily represent the views or policies of the Food and Drug Administration. The authors would like to thank Drs. Mamata Gokhale, Diane Wang, and Michael Fossler for their assistance in data collection during the early phase of this work. The authors would also like to express their gratitude for the helpful comments made by the reviewers of this paper.

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