IMPACT OF TRUNCATED AREA UNDER THE CURVE ON FAILED BIOEQUIVALENCE STUDIES: A COMPUTER SIMULATION ANALYSIS

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SUMMARY

The common measures used in a bioequivalence study are area under the curve (AUC) and the maximum plasma concentration. Estimation of AUC requires frequent blood samples. For long half-life drugs, sampling for long periods of time may become cumbersome. To resolve this issue some investigators have suggested the use of truncated AUC in bioequivalence studies for long half-life drugs. The suggested length of time for the truncated AUC is 72 hours. Many studies have been conducted to show that truncated AUC till 72 hours is a suitable approach. However, the suitability of truncated AUC for failed bioequivalence study has not been demonstrated. This report of simulated plasma concentration versus time data evaluates the suitability of truncated AUC for failed bioequivalence study of two

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hypothetical drugs. The results of the study indicate that the truncated approach for the estimation of the AUC for long half-life drugs in bioequivalence studies may be useful but it also increases the probability of accepting drugs as being bioequivalent when they are not.

KEY WORDS

bioequivalence, long half-life drugs, truncated AUC, confidence interval

INTRODUCTION

Bioequivalence studies are conducted to determine the therapeutic equivalence of drug products following the modification of an existing formulation or a generic formulation of an innovator's product. Bioequivalence trials are less resource intense than clinical trials and are commonly used in regulatory settings. For bioequivalence studies, it is assumed that the test and the reference formulations contain the pharmaceutically equivalent drug in the same dosage form (immediate or controlled release) and are administered by the same route. Bioequivalence studies are conducted under similar conditions (fasted or fed, single or multiple dose, healthy inviduals or patients). The common measures used in a bioequivalence study are area under the curve (AUC) and maximum plasma concentration (C_{max}) /1/. The use of these two pharmacokinetic parameters in bioequivalence studies is well established but a debate persists over the length of time for which AUC should be measured for long half-life drugs. Many investigators have suggested the use of truncated AUC in bioequivalence studies for long half-life drugs /2-4/. The suggested length of time for the truncated AUC is 72 hours /2/. The 72-hour sampling scheme has been mainly tested on products which are bioequivalent. However, the suitability of truncated AUC for failed bioequivalence study has not been demonstrated. In other words, if AUC calculated based on extensive sampling for a bioequivalence study is not within the 80-125% confidence interval, will the AUC estimated on 72-hour sampling give the same results? This report by simulated plasma concentration versus time data evaluates the suitability of truncated AUC for failed bioequivalence study of two hypothetical drugs. The

study ignores the impact of truncated sampling scheme on the C_{max} because for the majority of drugs C_{max} is reached much earlier than 72 hours and will not be influenced by such a scheme.

METHODS

Pharmacokinetic simulation

The one compartment first order absorption model was used to generate plasma concentrations versus time data (n = 24) for two hypothetical drugs. The simulations were performed on NONMEM (version 4, level 2, double precision). The pharmacokinetic parameters used in the generation of plasma concentration versus time data were absorption rate constant (K_a), volume of distribution of the central compartment (V), and clearance (CL). The model used was Advan 2 and Trans 2 with an exponential random residual error. For the simulation, the K_a for both reference and test product was kept similar so that the C_{max} for the two formulations is bioequivalent. The mean values of pharmacokinetic parameters with their associated coefficients of variation (CV) were as follows:

Drug A:

Reference:

$K_a = 1.20\ h^{-1}$, CV = 25%

V = 86 liters, CV = 20%

CL = 1.5 liters/h, CV = 20%

Test:

$K_a = 1.20\ h^{-1}$, CV = 25%

V = 86 liters, CV = 20%

CL = 1.05 liters/h, CV = 20%

The residual variability for both the reference and the test was 10%.

The mean half-lives for the reference and the test products were 40 hours and 56 hours, respectively. The dose was 500 mg and the plasma concentrations were expressed as μg/ml. The sampling schedule was 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, and 192 hours following the administration of drug.

Drug B:

Reference:

K_a = 1.20 h^{-1}, CV = 25%

V = 260 liters, CV = 20%

CL = 1.5 liters/h, CV = 20%

Test:

K_a = 1.20 h^{-1}, CV = 25%

V = 260 liters, CV = 20%

CL = 1.05 liters/h, CV = 20%

The residual variability for both the reference and the test was 10%.

The mean half-lives for the reference and the test products were 120 hours and 172 hours, respectively. The dose was 500 mg and the plasma concentrations were expressed as μg/ml. The sampling schedule was 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, 240, 288, 360, 480, and 600 hours following the administration of drug.

For both hypothetical drugs, the AUC was calculated by the trapezoidal rule, and the C_{max} was the highest plasma concentration observed on the plasma concentration versus time curve.

In order to generate plasma concentration versus time data, the clearance and half-life values of the hypothetical drugs are different. This was done intentionally so that the plasma concentration versus time data would be different from each other in a way that the bioequivalent study would fail for a given hypothetical drug. In addition, in this study, simulation was done till the time point when the last concentration becomes almost zero. Therefore, the estimated AUC (0-last) is almost equal to the AUC (0-∞).

Bioequivalence was assessed using the 90% confidence interval of the ratio of test to reference calculated using log-transformed data (two one-sided test) for both drugs /5/.

RESULTS AND DISCUSSION

Tables 1 and 2 summarize the AUC values and the confidence intervals for drugs A and B at different cut-off points. Sampling till 192 hours for drug A indicates that there is 29% difference between

TABLE 1

Arithmetic mean AUC values for drug A and associated confidence intervals (CI)

	Mean ± SD AUC (μg*h/ml)		% difference*	90% CI
	Test	**Reference**		
AUC (0-192)	454 ± 114	356 ± 113	29	126-135
AUC (120)	373 ± 78	308 ± 81	21	119-128
AUC (0-72)	276 ± 56	240 ± 54	15	113-120

* % difference = (test-reference)*100/reference

TABLE 2

Arithmetic mean AUC values for drug B and associated confidence intervals (CI)

	Mean ± SD AUC (μg*h/ml)		% difference*	90% CI
	Test	**Reference**		
AUC (0-600)	453 ± 132	340 ± 125	33	132-140
AUC (0-360)	387 ± 112	305 ± 98	27	125-132
AUC (0-240)	316 ± 78	262 ± 72	21	119-125
AUC (0-72)	134 ± 34	124 ± 31	8	106-109

* % difference = (test-reference)*100/reference

the test and reference formulation, and the 90% confidence interval is between 126% and 135%, which indicates that drug A fails to meet the bioequivalence criteria of 80-125%. When the AUC was calculated based on the 72-h sampling, the difference between the test and reference formulation was only 15%, and the 90% confidence interval is between 113% and 120%, which indicates that drug A passes the bioequivalence criteria of 80-125%.

For drug B, a similar trend was noted. The AUC calculated based on 600-h sampling produced 33% difference between the test and reference formulation with a confidence interval of 132-140%. The AUC (0-72) for drug B differed by only 8% between the test and reference formulation with a confidence interval of 106-109%.

These observations indicate that the truncated AUC (especially till 72 hours) may increase the chances of accepting drugs as being equivalent when in fact they are not. Furthermore, truncation of AUC for two and three half-lives indicated that the truncation should be done for at least three half-lives of the test compound to avoid the chances of accepting drugs as being equivalent when they are not.

The truncated approach for the estimation of the AUC for long half-life drugs in bioequivalence study may be useful but it also increases the probability of accepting drugs as being bioequivalent when they are not. The above two examples clearly demonstrate the limitations of this approach. This is probably not surprising as one can see from Tables 1 and 2 that the truncated areas in fact reduce the difference between the test and reference product which may result in accepting non-equivalent formulations as equivalent. Therefore, one should be cautious when interpreting bioequivalence studies based on the truncated AUC approach.

The conclusions made in this report are based on limited as well as simulated data. A definitive conclusion must be made based on real data (failed bioequivalence studies) using both low and high variable drugs.

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