Evaluation of Bioequivalence of Highly Variable Drugs Using Monte Carlo Simulations. I. Estimation of Rate of Absorption for Single and Multiple Dose Trials Using Cmax[1]

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Purpose. A Monte Carlo simulation study was done to investigate the effects of high intrasubject variation in clearance (CL), and volume of distribution (V) on the calculation of the 90% confidence interval (CI) for Cmax for single dose and multiple dose studies.

Methods. Simulations were done for both immediate release and sustained release scenarios. The simulated data were compared with clinical data from bioequivalence studies performed on indomethacin and verapamil.

Results. Previous reviews and simulations have shown that the probability of failure for the Cmax for single dose studies was always greater than that for multiple dose studies. However, the results for the simulated scenarios currently investigated indicate that if intrasubject (period-to-period) variation in CL and V is high (% CV's above 25%, and 12%, respectively), multiple dose studies can exhibit a higher probability of failure for Cmax than do single dose studies. Furthermore, Cmax values from studies performed with a sustained release scenario are more sensitive to changes in Ka, CL, and V than are results of studies on immediate release products. As an example, the probability of failure for immediate release products in simulated single dose studies is about 11% and 21% when the mean difference in Ka is 10% and 20%, respectively; while, the probability of failure for multiple dose studies is about 36% regardless of the difference in Ka. The corresponding values for the probability of failure for sustained release products were 25%, 53% for single dose studies and 39% for multiple dose studies. The simulations also indicate that changes in the fraction absorbed have a greater effect on the estimation of Cmax in multiple dose regimens than in single dose studies.

Conclusions. The results from these investigations indicate that multiple dose studies do not necessarily always reduce variability in Cmax.

KEY WORDS: bioequivalence; highly variable drugs; absorption rate; Monte Carlo simulations; single dose bioequivalence trials; multiple dose bioequivalence trials.

INTRODUCTION

It is a current regulatory practice to determine the bioequivalence of two drug products based on the 90% confidence intervals for the mean observed maximum concentration (Cmax) and mean area under the concentration time curve (AUC) ratios (test/reference). Products are considered bioequivalent if the confidence intervals for both parameters are within the range of 0.8–1.25 of the reference.

The determination of bioequivalence for highly variable drugs, those with intrasubject (period-to-period) coefficient of variation (CV) greater than 30%, has recently received increased attention. Such high intrasubject variability leads to the frequent failure of bioequivalent drug products since the confidence interval falls outside the acceptance criteria (1–3). An increase in subject number sufficient to markedly improve the 90% confidence interval is usually considered too expensive.

Several changes in study design have been proposed to overcome the difficulty of assessing the in vivo bioequivalence of highly variable drug products (1). Among the suggestions are:

1. Determine bioequivalence at steady-state, rather than after single dose administration, since multiple dose studies are believed to reduce the intrasubject variability.

2. Employ replicate study designs to evaluate intrasubject variation for the test and reference product.

3. Use simultaneous dosing of stable isotopes to correct for intrasubject variation and thus reduce the number of subjects needed to assess bioequivalence. For this design an intravenous, or more often an oral solution, dosage form containing the stable isotope labeled drug is administered concomitantly with the test and again with the reference product. The parameters derived from the labeled drug are used to normalize the bioequivalence parameters for factors not related to the dosage form.

4. Use sequential addition of group of subjects (add-on study designs) with proper adjustment of the statistical significance levels of the associated hypothesis tests to minimize total subject number. For example, an initial group of 20 subjects might be studied and, based on the results, a decision be made to declare the products bioequivalent, not bioequivalent or to continue the study with a second group of subjects. The decision criteria must be specified prospectively.

In a recently published study, simulated and clinical data were used to examine the issue of Cmax in single versus multiple dose bioequivalence determination for drugs that have intrasubject CV's in clearance of less than 20% (4). We have extended the investigation of the relationship between single and multiple dose studies to the category of highly variable drugs and have examined the influence of dosage form, immediate release vs. sustained release, in an effort to better define the impact of multiple dosing on the probability of passing a bioequivalence test for Cmax i.e. that the 90% confidence interval for the least square mean of the test-to-reference ratio lies between 0.8 and 1.25 (reference).

METHODS

Examples of Bioequivalence Studies

Single and multiple dose clinical trials for indomethacin and verapamil (the data obtained from drug studies submitted to the Office of Generic Drugs, FDA) were evaluated for bioequivalence. The subjects in the study were males between the ages of 18–45 and who were within 15% of the

[1] The views expressed in this paper are those of the authors and do not necessarily represent the policy of the Food and Drug Administration.

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ideal body weight. The healthy volunteers participated in single and multiple dose studies employing two-treatment, two period, randomized crossover designs. A one-week washout period was used between doses for the single dose studies. However, there was no washout period between treatments for the steady state studies.

A summary of study details is presented in Table 1.

Monte Carlo Simulations

The simulations were done assuming a one-compartment model with first-order absorption and elimination (5). Each subject received one single 500 mg oral dose or multiple 500 mg oral doses at equally spaced intervals. The dose was constant in all simulation studies. Blood sampling times for immediate release (IR) single dose administration were: 0.0, 0.5, 1, 2, 4, 8, 16, 24, and 36 hours post-dose. The sampling times for multiple dosing (8h dosage regimen) were: 0.0, 0.5, 1, 2, 4, 6, and 8 hours post-dose. Sampling times for sustained release products were extended to 48 hours for single dose studies. A 12 hour dosing interval was chosen for the multiple dose sustained release studies and the following sampling times were used: 0.0, 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose. The random error for drug concentration at each sampling time was assumed to be log-normal with a 15% CV. This error accounts for assay error and model mis-specification error.

Four scenarios were employed to study the effect of intrasubject variability on immediate release and sustained release formulations.

Scenario I: Immediate Release Formulations

Bioavailability (F) and a first order absorption rate constant (Ka) were assumed to be equal for both the test and the reference. i.e. the same drug formulation was readministered to each subject.

Eight designs were created using four different levels of intrasubject variability and two study designs (single and multiple dosing). Each unique set of conditions formed the basis for a 30-subject bioequivalence trial which was repeated 1000 times.

Scenario II: Immediate Release Formulations

Bioavailability (F) was assumed to be equal for both the test and the reference. There were three Ka ratios, four levels of intrasubject variability in clearance (CL) and volume of distribution (V), and two study designs (single and multiple dosing). This produced 24 unique combinations of pharmacokinetic factors and parameters.

Scenario III: Sustained Release Formulations

The same as Scenario II, but sustained release products were simulated by assigning lower values to the mean Ka's and longer sampling times.

Scenario IV: Immediate Release Formulations

Fifteen different situations were created by combining three different levels of intrasubject variability with five different levels of F for the test/reference ratio (assuming $F_{ref} = 1$), while holding the difference in Ka at a 10% level (Ka1) for both single dose and multiple dose studies. This scenario produced 30 unique sets of conditions.

The four scenarios produced 86 different situations and the Monte Carlo simulations were repeated 1000 times for each situation. PK analysis and statistical evaluation were performed on the concentration-time profiles of over 2,580,000 simulated volunteers.

Stochastic variation in Ka, CL, and V was introduced by a random number generator, rannor(0) in the SAS system, which creates a standard normal random deviate. For the purpose of simulation, a log-normal distribution for all these pharmacokinetic parameters was used. Intersubject variability in the pharmacokinetic parameters (CL, V, Ka) was introduced by sampling from the population log normal distribution. Intrasubject variability was added to each subject's disposition parameter values (CL, V) at each trial period and the parameters were assumed to be constant over that trial period. Intra-subject variability in CL and V was modeled by allowing CL and V to vary between treatments but for each parameter to be correlated ($\rho = 0.9, 0.75, 0.5$) within a given subject. Intrasubject variability for CL and V corresponding to these levels of correlation are 0.0% at level I, 15% and 8% at level II, 25% and 12% at level III, and 35% and 17% at level IV, respectively. In spite of the crossover design used, which should account for intersubject variability, it is quite possible that intersubject variability in a derived parameter such as observed Cmax could contribute to intrasubject variation, thus, intersubject variability was included to better mimic the real situation.

The difference between the two formulations was simulated by creating bivariate random deviates for Ka for the test and reference using high correlation ($p = 50\%$). These differences represented the different rate of absorption of the two treatments for each subject. A summary of the parameters and the different levels of variability used in the simulations are given in Table 2.

A symmetric factorial design was employed to include all possible combinations of the variables (ρ, CV) and the pharmacokinetic parameters of interest such as Ka, F, CL, and V. Sequence and period were assigned in a randomized balanced manner to mimic the usual two-period crossover bioequivalence study. Each unique combination of parameters and variables formed the basis of a specific design for a bioequivalence trial which was repeated 1000 times. Simulations were performed using SAS running on a SUN Sparc Station 1+.

Table 1. Summary of Study Details for the Single Dose (SD) and Multiple Dose (MD) Studies

	Indomethacin		Verapamil	
	SD	MD	SD	MD
Subjects	30	32	35	21
Dose (mg)[a]	75	75	240	240
Assay Range (ng/ml)	10-5000		5-500	
Assay CV (%)	2.5-6.3	2.8-5.8	2.3-5.3	2.6-6.2

[a] All multiple dose studies were done on the same lot of drug as used for the single dose study. Doses were mg/day.

Table 2. Mean Parameter Values and Their Levels of Variability for Simulation Designs

Ka1 (test, reference)	0.165, 0.15
Ka2	0.18, 0.15
Ka3	0.195, 0.15
Ka-CV%	50
ρ-Ka-intrasubject	0.50
F1 (test, reference)	1.0, 1.0
F2	1.05, 1.0
F3	1.1, 1.0
F4	1.2, 1.0
F5	1.25, 1.0
CL	0.86
CL-CV%	50
Intrasubject CL CV%	
(level I)	0.0
(level II)	15
(level III)	25
(level IV)	35
V	10
V-CV%	25
Intrasubject V CV%	
(level I)	0.0
(level II)	8.0
(level III)	12
(level IV)	17
Dose	500
τ	8
AI	2.0
sustained release products:	
Ka1 (test, reference)	0.09, 0.081
Ka2	0.09, 0.072
Ka3	0.09, 0.067
τ	12
AI	1.5

τ: Dosing interval, AI: Accumulation Index calculated as $1/(1-e^{-k\tau})$.

Assay error (15%) was added to the resulting plasma concentration-time profiles generated for each subject and dosing period. Cmax was observed directly from the data, while area under the curve to the last measurable time point, AUC(0-t), was calculated using the trapezoidal rule. The AUC(0-inf) was estimated by adding to AUC(0-t) the calculated area Ct/kel where Ct is the last drug concentration and kel is the terminal elimination rate constant (5). For multiple dose simulations, the simulated concentrations values assumed ten doses to approximate attainment of steady-state. The AUC[(0) to τ] was calculated using the trapezoidal rule. All the resultant log-transformed parameters for each trial were analyzed by SAS (GLM) and the 90% confidence intervals for the test/reference ratios were calculated (6). The 90% confidence interval for each replication was compared to the range of 0.8–1.25. If either limit fell outside the range the products were declared to be "not equivalent" for that replication.

RESULTS

Figure 1(a, b) presents the distributions of difference in Least Square Means (LSM) of Ln Cmax values between the test and reference for single and multiple dose regimens based on scenario I. This scenario assumed that the test and reference have the same extent and rate of absorption with low and high levels of intrasubject variability (level II and level IV, respectively) in CL and V. In the case of the low intrasubject variability (Fig. 1a), variabilities in differences in LSM's are very similar between the single dose and multiple dose bioequivalence trials, SD's are 0.0488 and 0.0439, respectively. However, for the high intrasubject variability (Fig. 1b), the variability in differences in LSM's is greater for multiple dose than single dose bioequivalence trials, SD's are 0.0843 versus 0.0635, respectively. Thus, any single study conducted at steady state could have a higher probability of failure, for Cmax, than would a single dose study.

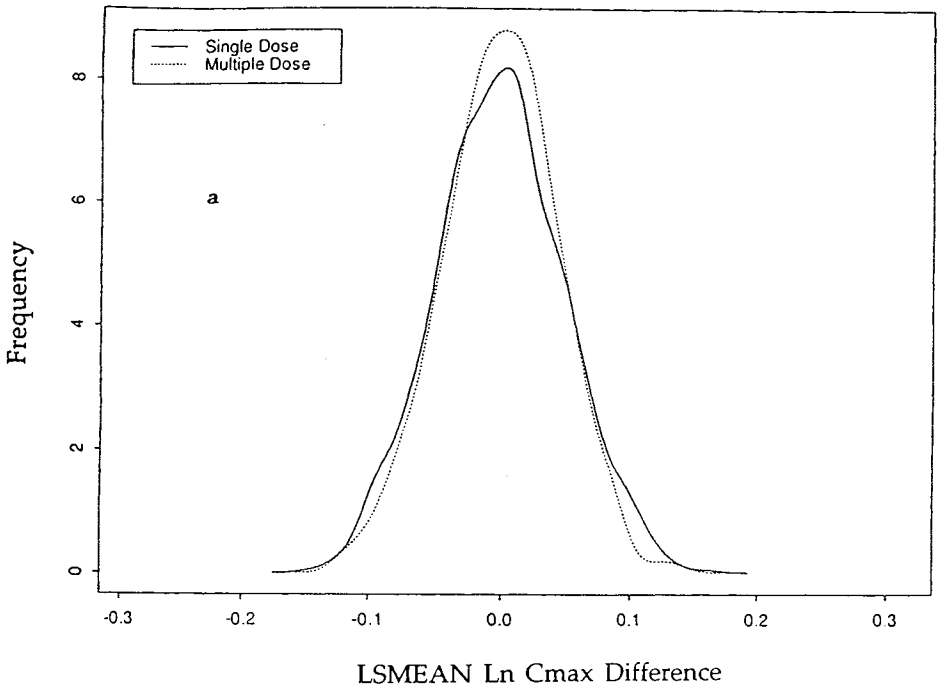
The purpose of the simulations of scenario I was to understand the underlying mechanism of the behavior of Cmax at different levels of intrasubject variability for single dose and multiple dose studies. Intrasubject CV's of Cmax for these design were estimated and found to be 15.90% and 14.24% for single dose and multiple dose, respectively in the case of low intrasubject variability. For high intrasubject variability, the CV's rose to 20.21% and 27.17%, respectively, with the CV for multiple dose being greater than single dose.

When the test and reference formulations are the same we should expect LSM to be near zero and it is desired that the probability of failure be very minimal. Figure 2 shows that Cmax for multiple dose incorrectly fails the bioequivalence test (38%) when the intrasubject variability in CL and V are high (35%, 17%, respectively). This illustrates that variability in Cmax at steady state is a more influenced by the variability in disposition.

Figure 3 shows the influence of the increasing levels of intrasubject variation in CL and V on the probability of passing or failing the bioequivalence test for the immediate release formulation. The probability of failure for Cmax is higher for single dose than multiple dose when intrasubject variability in CL and V are low, but at or above a level III variation in CL and V (i.e., 25% and 12% intrasubject variability, respectively), the probability of Cmax failure becomes greater following multiple dose when the Ka1 and Ka2 ratios were assumed. A power curve constructed from these simulations from scenario II shows that with increasing intrasubject CV in CL and V, the probability of failure for the multiple dose study eventually exceeds that for the single dose study for Ka1 and Ka2 but not for Ka3 (Fig. 4). The multiple dose immediate release studies display the same sensitivity to intrasubject variability in clearance and volume irrespective of the Ka ratio.

Simulations performed for the sustained release formulation using high levels of intrasubject variation in CL and V also exhibits a greater probability for failing the Cmax bioequivalence test as the level of intrasubject variation is increased (Fig. 5). On the other hand, an increased probability of failure for sustained release multiple dose compared to single dose is only observed for Ka1 (10% difference between test and reference Ka values). This is illustrated by the power curve in Figure 6, in which an increased probability of failure for Cmax with increasing variability in CL is observed only at the Ka1 level of Ka ratio.

For both immediate release and sustained release prod-



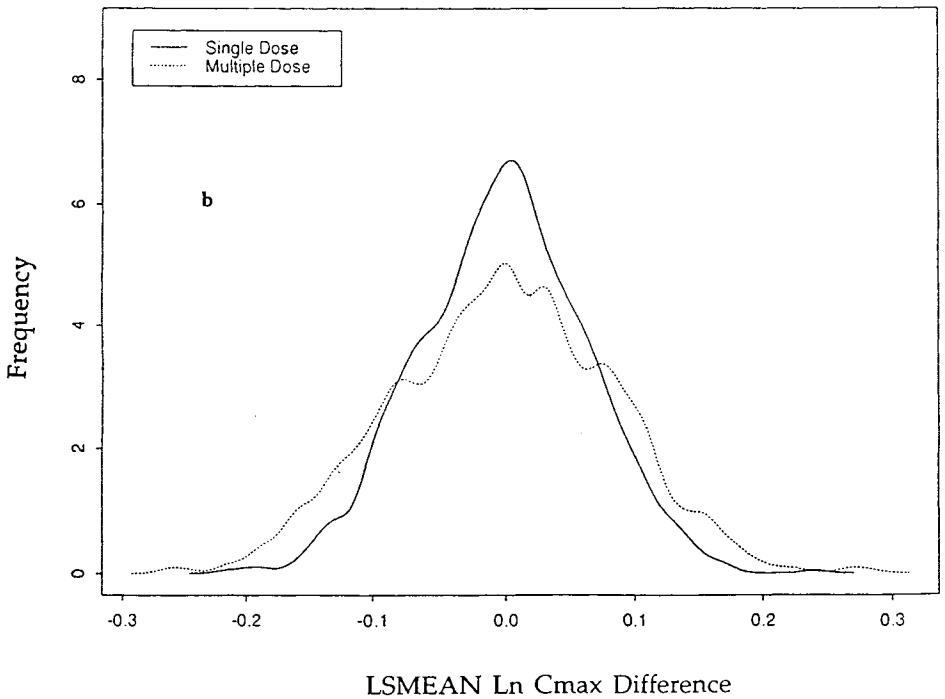


Fig. 1. Frequency distributions of LSM of Cmax for 1000 bioequivalence trials simulated for single dose and multiple dose. The conditions employed in these specific designs were scenario I with no difference in Ka or F between the test and reference. Fig. 1a represents the case of low intrasubject variability in CL and V (CV of 15% and 8%, respectively). In contrast, Fig. 1b shows the distribution in the case of high intrasubject variability in CL and V (CV of 35% and 17%, respectively).

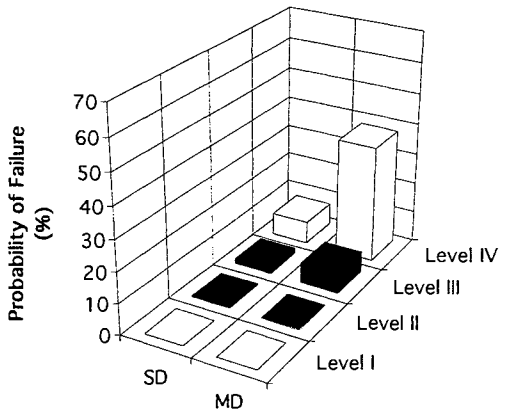


Fig. 2. Probability of failure of LCmax for single and multiple dose studies for an immediate release formulation at Ka ratio test/reference of one (0.195/0.195) and 4 levels of intrasubject variability in clearance (level I = 0.0%, level II = 15%, level III = 25%, level IV = 35%). Intrasubject variability in volume values are approximately 50% of those for clearance in the corresponding levels.

ucts, the probability of multiple dose studies failing the Cmax bioequivalence criterion rises rapidly when the variability in CL is greater than 25% and this is independent of the differences in absorption rate.

In simulation scenario IV, the effect of changing the fraction available (F) for the test formulation on the probability of failure of Cmax was investigated at different levels of intrasubject variability for immediate release formulations following single dose and multiple dose (Fig. 7). When the F ratio was greater than 1.2, the probability of failure of Cmax was almost 100% for single dose and multiple dose studies, irrespective of the level of intrasubject variability. The influence of intrasubject variability becomes more apparent when the F ratio is 1.2 or greater, with level IV (35% intrasubject variation) having the highest probability of failure for any

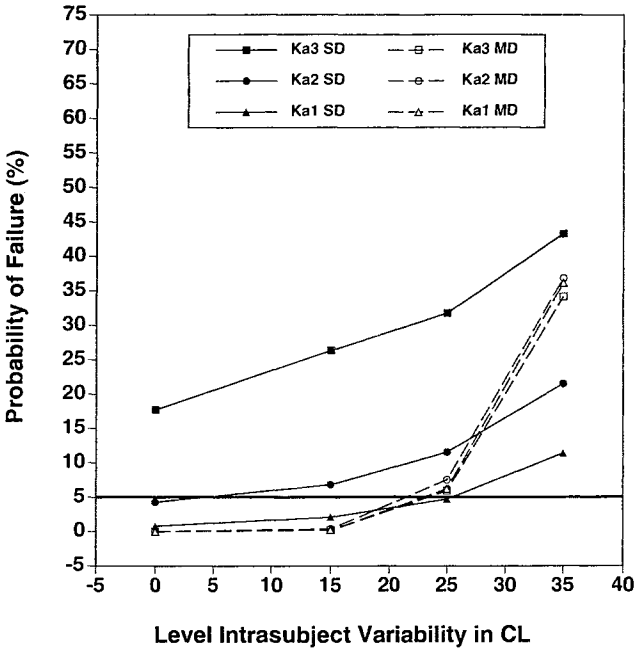


Fig. 4. Power curves of LCmax as a function of the level of intrasubject variability in clearance and volume. The Ka1 (triangles), Ka2 (circles) and Ka3 (squares) ratios are the same as for Figure 3. The filled and empty symbols are for single dose and multiple dose designs, respectively.

given F value. This effect was more pronounced for multiple dose studies than for single dose, as the power curves illustrate (Fig. 7). It is also interesting to note that multiple dose administration under the conditions of a 5–10% difference in F at level IV has a greater probability of failure for Cmax than does single dose administration. Also, when the test and reference products had equivalent extent of bioavailability, the multiple dose study was more likely than the single

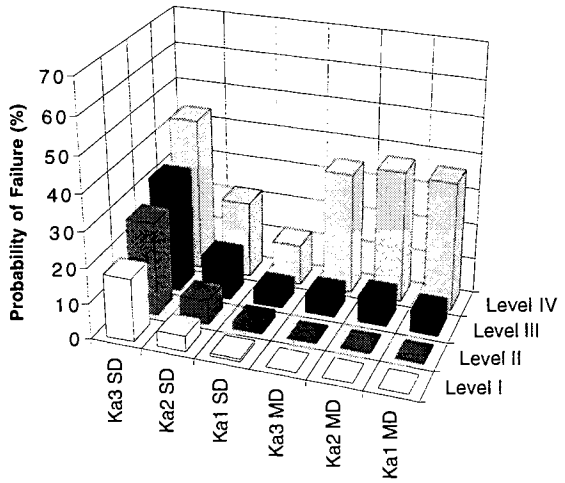


Fig. 3. Probability of failure of LCmax for single and multiple dose studies for an immediate release formulation at 3 Ka ratios test/reference (Ka1 = 0.165/0.15; Ka2 = 0.18/0.15; Ka3 = 0.195/0.15) and 4 levels of intrasubject variability in clearance (level I = 0.0%, level II = 15%, level III = 25%, level IV = 35%). Intrasubject variability in volume values are approximately 50% of those for clearance in the corresponding levels.

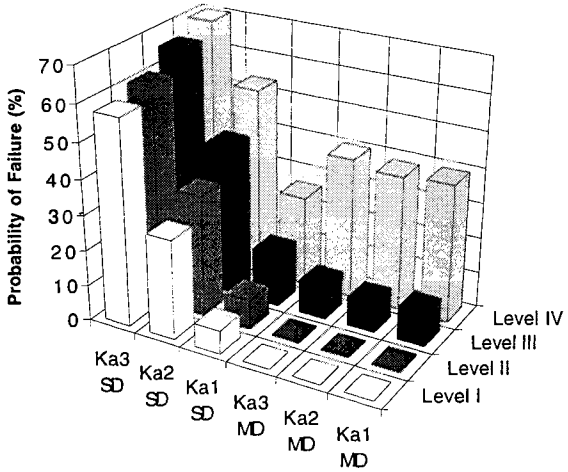


Fig. 5. Probability of failure of LCmax for single and multiple dose studies for an sustained release formulations at 3 Ka ratios test/reference (Ka1 = 0.09/0.081; Ka2 = 0.09/0.072; Ka3 = 0.09/0.067) and 4 levels of intrasubject.variability in clearance (level I = 0.0%, level II = 15%, level III = 25%, level IV = 35%). Intrasubject variability in volume values are approximately 50% of those for clearance in the corresponding levels.

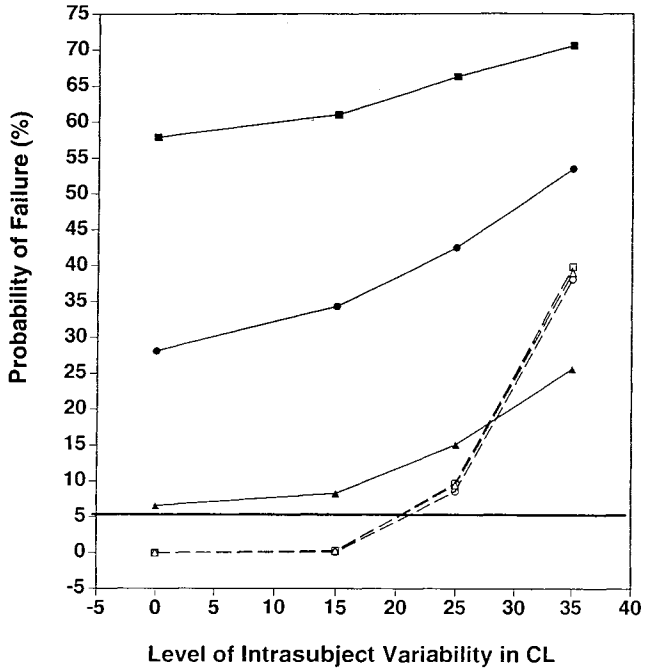


Fig. 6. Power curves of LCmax for sustained release formulations as a function of the level of intrasubject variability in clearance and volume. The Kal (triangles), Ka2 (circles) and Ka3 (squares) ratios are the same as for Figure 5.

dose study to fail Cmax when intrasubject variation was at level IV.

The clinical data for the indomethacin sustained release studies show the effect of intrasubject variation on the estimation of single and multiple dose confidence intervals for Cmax (Table 3). The experimental Cmax data for indomethacin had an estimated pooled intrasubject variation of 20–25% with less than 20% estimated difference in Cmax. Intrasubject CV and the difference in LSM for Cmax were higher for the multiple dose than for the single dose study.

Clinical data for verapamil is presented in Table 3. The data shows an increase in intrasubject variability accompanied with a parallel increase in the confidence interval range from single dose to multiple dose with the multiple dose confidence interval being clearly outside the acceptable range.

Power analysis was performed for scenario II with different acceptance criteria's for Cmax. When the acceptance limits for Cmax is widened from 80%–125% to 75%–133%, the probability of passing the Cmax acceptance criteria has increased for the formulations that are truly bioequivalent (Kal, Ka2 curves) as shown in Figure (8). However, the probability of passing the Cmax acceptance criteria is also increased for the formulation that differ by 30% in Ka values, for example compare Figures 4 and 8 for Ka3.

DISCUSSION

Data have been published discussing the relationship between single and multiple dose confidence interval's for immediate-release drugs with linear kinetics and high variability (7). The two drugs used as examples, were propafenone and verapamil. Propafenone had intrasubject variability for Cmax of 29% single dose and 16% multiple dose which resulted in 90% confidence interval for Cmax of 71–160% and multiple dose of 90–104%. A similar pattern was shown for immediate release verapamil. However, the results in the current manuscript show different outcomes based on the level of intrasubject variation. For the indomethacin sustained release formulation pooled intrasubject variability values of approximately 20% and 25% for single dose and multiple dose studies, respectively, were observed. For verapamil sustained release (table 3), the intrasubject variability for Cmax increased from 26% for single dose to 31% for multiple dose. This is in contrast to the referenced study (7) for an immediate release formulation which seemed to follow the pattern previously reported, (multiple dose

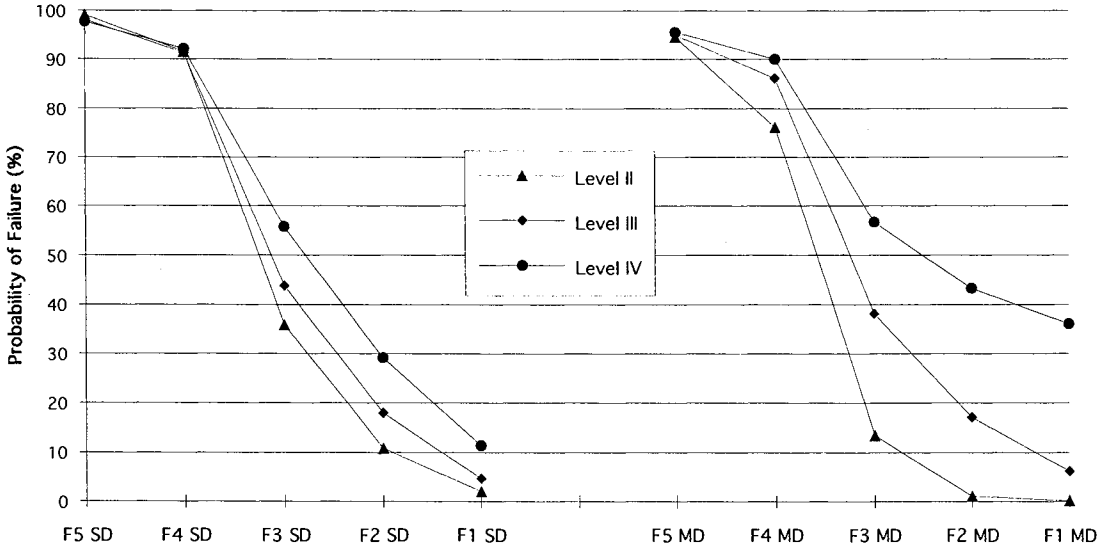


Fig. 7. Power curves of LCmax as a function of F ratios (F1 = 1, F2 = 1.05, F3 = 1.1, F4 = 1.2 and F5 = 1.25 for the test/reference ratio) and level of intrasubject variability (level II-15%, level III-25% and level IV-35% intrasubject variability).

Table 3. Comparative Intrasubject Variation (Intra), Estimate of Difference Between Means (Est), Standard Error of the Mean (See), and the LCmax 90% Confidence Intervals (CI) for Indomethacin and Verapamil Bioequivalence Studies

	Single Dose				Multiple Dose				
Mean	Intra	Est	See	CI	Mean	Intra	Est	See	CI
				Indomethacin					
T[a] 0.609	20.1	−0.105	0.055	79-99	0.91	25.2	−0.18	0.069	69-93
R[b] 0.714					1.09				
				Verapamil					
T[a] 4.9	26.5	−.086	0.0634	79-104	5.33	31.6	−0.0776	0.0975	75-109
R[b] 4.8					5.25				

[a] T: test.
[b] R: reference.

confidence interval being smaller than that for single dose) for immediate release drugs that exhibit low intrasubject variability (4). It is apparent that the confidence interval of verapamil at multiple dose is wider (34 vs 25) due to the obvious increase in the intrasubject CV. The data for indomethacin and verapamil show an increase in the probability of the multiple dose study failing the Cmax confidence interval criterion with increasing intrasubject variability, as predicted by the simulated power curves. Based upon the simulations, there is an increase in the probability for multiple dose studies to fail once intrasubject variability for CL exceeds 25%. This agrees with the observations for the sustained release verapamil and indomethacin studies which had a higher failure rate for Cmax in multiple dose versus single dose when intrasubject variation was above 25%. It is apparent that the sustained release and immediate release dosage forms may be far more sensitive following multiple dose than after single dose to intrasubject differences in clearance and volume as seen by the superimposability in each figure of the multiple dose power curves, irrespective of the Ka value (Fig. 4 and 6). It is also useful to point out that at any given level of intrasubject variability and Ka ratio, the sustained release formulation has a higher probability of failure.

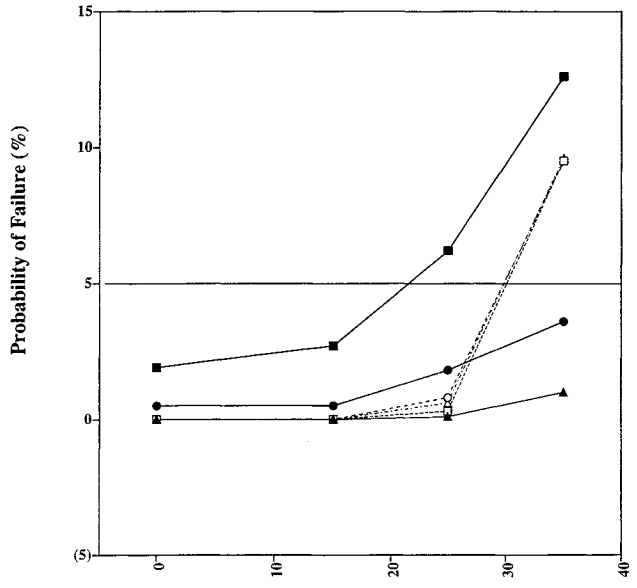


Fig. 8. Power curve of LCmax as a function of intrasubject variability in clearance and volume with an acceptable confidence interval of 75–133. Symbols are the same as for Figure 4.

It has been suggested that a possible solution to the problem of highly variable drugs would be to use a multiple dose regimen whenever ethically feasible (7). However, based upon the results from this study, one would not necessarily achieve the goal of less intrasubject variability, as suggested by Blume, especially when using a sustained release formulation. As apparent from the simulated and the indomethacin and verapamil data, the multiple dose study may exhibit greater sensitivity to clearance for the sustained release dosage form even when the true differences in Ka are small. If a measure of rate of absorption other than Cmax was used, one that reflected only true rate of input, rather than input and disposition, as is measured by Cmax, it is possible that the observed increase in the probability of failure of the multiple dose trial would not occur. These studies suggest that the comparison of highly variable drugs may not be facilitated by multiple dose studies.

Another possible resolution to the problem of highly variable drugs may be accomplished by setting a wider range for the acceptance criteria. This would increase the probability of the Cmax value meeting the acceptance criterion for formulations that are truly bioequivalent. The range should be widened only for drugs of suitably large therapeutic indices and high intrasubject variability. For drugs of unknown intrasubject variability, replication of the design may be needed to justify the assumption of high intrasubject variability.

Other alternatives are also worth considering. These include the selection of the best measure of absorption rate based on simulation of the particular situation in bioequivalence trials (8), and indexing of criteria to reference product variability and therapeutic index (9).

CONCLUSIONS

The simulation studies clearly showed that the probability of failure of Cmax is sensitive to the magnitude of intrasubject variability in disposition. First, the definition of

highly variable drug products as products that exhibit intra-subject variability more than 30% is confirmed. Second, the probability of failure of Cmax can be greater in multiple dose studies than in single dose studies when there is high intra-subject variability in disposition. Third, Cmax measured in multiple dose studies is much less sensitive to real differences in the rate of absorption than when measured in single dose studies. This inability to detect differences in rate of absorption was consistent regardless of the level of intra-subject variability in disposition. Fourth, a small increase in the acceptance criteria (80–125 to 75–133) may produce a large decrease in the probability of failure for highly variable drugs.

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