Comparison of Single and Multiple Dose Pharmacokinetics Using Clinical Bioequivalence Data and Monte Carlo Simulations

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The purpose of this study was to evaluate the relative performance and usefulness of single dose (SD) and multiple dose (MD) regimens for bioequivalence (BE) determination. Drugs such as indomethacin, procainamide, erythromycin, quinidine, nifedipine were tested for BE under SD and MD dose regimens. Drugs characterized by low accumulation indices (AI) showed virtually no change in the 90% confidence interval (CI) of AUC and CMAX upon multiple dosing. On the other hand, drugs with higher AI appeared to have smaller CI at steady-state. For example, the CI range of AUC and CMAX of quinidine (AI of 1.54) decreased from 26 to 12 and from 22 to 12, respectively, upon multiple dosing. A Monte Carlo simulation study of SD and MD bioequivalence trials was performed. The probability of failing the bioequivalence test was evaluated for several situations defined by different levels of variability and correlation in ka constants, presence or absence of inter- and/or intra-individual variability in clearance (CL) and volume of distribution (V), and different degrees of accumulation. All the possible combinations of these factors were tested with SD and MD study designs. All simulations used 1000 data sets with 30 subjects in each data set for a total of 144 unique designs (total of 144,000 simulations of bioequivalence trials). Upon multiple dosing, narrowing of CI ranges was observed for drugs simulated to have high AI, high variability and a large difference in absorption constants (ka) between test and reference formulations. The mean AUC and CMAX CI ranges for this situation decreased from 15 to 6 and from 16 to 10, respectively, in going from SD to MD design. Thus, there was concordance between simulated and experimental data. The probability of failing the bioequivalence test is shown to dramatically decrease upon multiple dosing due to the changes (range and shift) in the confidence interval.

KEY WORDS: bioequivalence; absorption rate; steady-state bioavailability; Monte Carlo simulations.

INTRODUCTION

Since the implementation of the Drug Price and Patent Term Restoration Act in 1984 the U.S. Food and Drug Administration (FDA) has established the bioavailability and bioequivalency requirement for generic substitution (1,2). The aim of the clinical bioavailability studies is to compare certain pharmacokinetic parameters of the test with the reference product. The current bioequivalence test requires that the population mean difference in the extent (AUC) and rate of absorption (CMAX) between the test and reference formulation does not differ by more than 20% to declare bioequivalence.

An important issue in determining bioequivalence is the choice of single- vs. multiple-dose trials. Although SD pharmacokinetics (PK) should be predictive of MD given linear kinetics (3–7), the PK parameters used to assess BE under steady-state (SS) versus non-SS conditions, especially those related to absorption rate, are not always the same. Products sometimes fail to meet BE criteria when given as a single dose but pass the criteria when dosed to steady-state. The choice between SD and MD design remains very controversial. SD studies are believed to be more sensitive for detecting change in rate and extent of absorption. However, multiple dose studies are often more representative of clinical drug use. It is recognized that CMAX is a poor indicator of rate of absorption for single dose studies (8). It is expected that CMAX will be an even worse indicator of rate in multiple dose studies.

It is the purpose of this paper to examine the influence of various variabilities that are encountered in clinical bioequivalence trials on the confidence interval and ultimately on the probability of passing or failing the bioequivalence test. To illustrate the difference in SD and MD-based BE determination, data from several BE studies were reanalyzed using SAS and the two one-sided test procedure (9). Due to the complex interaction and multiple effects of inter- and intra-subject variability, study design, and magnitude of difference in absorption rate, a more rigorous evaluation using simulated data was performed to assess their impact on BE decision making. The pharmacokinetic analysis and the statistical evaluation for over 2,160,000 simulated volunteers was performed twice; once for single dose studies, and again for multiple dose studies.

METHODS

Bioequivalence Study Protocols

Bioequivalence study data from single and multiple dose clinical trials for nifedipine, indomethacin, erythromycin, procainamide and quinidine (obtained from ANDA drug studies submitted to Office of Generic Drugs) were reevaluated. All subjects in these studies were males between the ages of 18 and 45 years and within 15% of the ideal body weight. The healthy volunteers participated in two-treatment, two-period, randomized crossover single and multiple dose studies. A one-week washout period was used between doses for each of the single dose studies. However, there was no washout period between treatments for the steady-state studies.

Details for each drug and design are presented in Table 1.

Monte Carlo Simulations

The simulations were done assuming a one compartment model with first-order absorption and elimination. The design was for each subject to receive one single oral dose (500 mg) or multiple (500 mg) doses at equally spaced intervals. The dose was assumed to be constant in all simulation studies. The model represents a drug with a half-life of 8

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Table I. Study characteristics for indomethacin, nifedipine, erythromycin, quinidine, and procainamide

		Subjects	Dose (mg)	Assay CV (%)	LOQ (ng/ml)
Indomethacin	SD	20	75	5.6	100
	Md	20			
Nifedipine	SD	19	10	8.0	5
	Md	14			
Erythromycin	SD	35	250	7.0	50
	MD	35			
Quinidine	SD	24	324	6.9	50
	Md	19			
Procainamide	SD	24	500	6.2	50
	Md	20			

SD: single dose, MD: multiple dose, LOQ: limit of quantitation.

hours. Sampling times for single dose administration were: 0.0, 0.5, 1, 2, 4, 8, 16, 24, and 36 h. The sampling times for multiple dosing were different for different dosing regimens. For a dosing interval of 36h. the sampling times were: 0.0, 0.5, 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 32, 36; for a dosing interval of 12h., the sampling times were: 0.0, 0.5, 1, 2, 4, 6, 8, 12; for 8h. dosage regimen, the sampling times were: 0.0, 0.5, 1, 2, 4, 6, 8. The random error for drug concentration at each sampling time was assumed to be log-normal with a 15% CV.

Three major scenarios based on the presence or absence of inter- and intra-subject variability in CL and V were investigated.

Scenario I

CL and V were held as constant parameters at fixed values, i.e. there was neither inter- nor intra-subject variability in these parameters. The only source of error was in the analytical method.

Scenario II

CL and V were introduced into the model with inter-subject CV of 50% and 25% respectively, but there was no intra-subject variability in these parameters.

Scenario III

Intra-subject variability in CL and V was added to the model in scenario II by allowing CL and V to vary between treatments but to be highly correlated ($\rho = 0.9$) within a given subject. These variabilities were estimated using NONMEM (Version 4.0) and found to be 17.9% for CL and 8.9% for V. A log-normal statistical model was used in PRED (10) to calculate the population intra-individual CV for 1000 individual values of CL and V for the two-period treatment. Stochastic variations in ka, CL, and V were introduced by random number generator, rannor (0) in SAS system which creates a normal random deviate with a mean of zero and standard deviation of one. The availability factor (F) was set equal to 1 for all simulations. For the purpose of simulation, a log-normal distribution for all these pharmacokinetic parameters was used. Bivariate random deviates for absorption constants for the test and reference were created using high and low correlations (p) 50% and 25%. Three levels of AI (1.05, 1.5, 2) and two different ka coefficients of variation, 25 and 50%, were introduced to study their effect on the estimation of the relevant pharmacokinetic parameters. A summary of the parameters and different levels of variability used in the simulations is given in Table II.

All possible combinations of the variables (P, AI, CV) and the pharmacokinetic parameters of interest e.g. ka, CL, V were considered. A symmetric, complete factorial design was employed such as at each level of a given pharmacokinetic factor (or independent variable) was combined in turn with every level of the other factors in the experiment. Sequence and period were assigned in a randomized balanced manner to mimic the usual two-period crossover bioequivalence study. Each unique set of parameters and variables formed the basis for a 30-subject bioequivalence trial which was repeated 1000 times. Simulations were performed using SAS running on a SUN Sparc station 1+.

Symbols and abbreviations for the simulations are given in Appendix I. The resulting data were used to estimate the bioavailability parameters of CMAX and, AUC. 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(t − ∞) was estimated by adding to AUC (0 − t) the calculated area Ct/λ where Ct is the last drug concentration and λ is the terminal elimination rate constant (6). For multiple dose simulations, sampling was done after the tenth dose to assure steady-state. The first concentration-time point was at time of dose and the last concentration-time point was at τ and the AUC [(t) − (t + τ)] was again calculated using the trapezoidal rule.

All the resultant parameters for each trial were consequently analyzed by SAS (GLM) and the 90% confidence interval for the test/reference ratio was calculated (9). Inequivalence for a specific replication occurred when the 90% CI extended outside the range of 80–120%.

Table II. Mean parameter values and their levels of variability for simulation designs

ka (test/reference)	0.375/0.15, 0.375/0.281
ka-CV%-intersubject	25, 50
ρ-ka-intrasubject	0.25, 0.50
CL	0.86
CL-CV%-intersubject	0.0, 50
ρ-CL-intrasubject	0.90
V	10
V-CV%-intersubject	0.0, 25
ρ-V-intrasubject	0.90
F	1.0
Dose	500
AI	1.05, 1.5, 2.0

There are a total of three scenarios, three values of AI, two levels of correlation of ka (ref., test), two levels of variability in absorption constants, two levels of absorption constant ratio (test/reference), and two designs for single and multiple designs regimens. This produced one hundred forty four unique combinations of pharmacokinetic factors and parameters for clinical trials. The Monte Carlo simulations were repeated 1000 times for each situation.

RESULTS

Bioequivalence Clinical Studies

The bioavailability parameters of indomethacin, procainamide, erythromycin, quinidine, and nifedipine for SD and MD studies are summarized in Table III, and IV. Upon multiple dosing, the estimates of the mean difference in CMAX between test and reference decreased for all drug studies, except indomethacin. The absolute decrease in the mean difference from SD to MD was also accompanied with narrowing in the CI's for erythromycin, quinidine, and procainamide. These changes enabled erythromycin, quinidine and procainamide to meet the CI criterion after failing the SD study. These three drugs have accumulation indices ranging from 1.22 to 1.76.

The CI of AUC for the same drugs followed a similar trend although the effect was less pronounced. Quinidine was the only drug to fail CI criteria for AUC in the SD study, but it passed in MD study due to a decrease in the mean difference and the standard error.

Monte Carlo Simulations

The performance of the two-one sided test requirement indicated that the probability of the test product not passing the bioequivalence test was greater when both test and reference products had high coefficients of variation for ka. Moreover, a test product compared to a reference product with equal coefficient of variation but higher degree of correlation between the test and the reference had less probability of failure.

The mean upper and lower limits of the CI of CMAX for each of the simulated bioequivalence designs in Scenario II, and III are depicted in Figure 1. The behavior of the CI of CMAX in scenario II was very similar to scenario I. Multiple dosing induced a consistent downward shift in the boundaries of the CI in all scenarios (Figure 1). Figure 1a shows that the mean upper level of the CI for all SD designs is very close to the upper boundary of the acceptable limit with around 30% of individual upper CI values crossing that boundary. The small shift that occurs with MD even in the presence of minimal accumulation is sufficient to decrease the probability of failure to less than 10%. The shift was more pronounced for drugs that accumulate upon multiple dosing and for which there was a large difference in ka values (Figure 1c, d).

Comparing the low ka ratio (Figure 1a, b) to the high ka ratio (Figure 1c, d), it is clear that the low ratio of 1.3 yields mean upper limits below 120 for both single and multiple doses where as the higher ratio of 2.5 yields a more complex pattern.

A noteworthy observation was the narrowing in the CI related to changes in sources of variability. Only in scenario III (Figure 1a, c) where we assumed inter- and intra-individual variability in CI and V we can observe that there was no decrease in the width of the CI accompanied with the aforementioned shift. In the other scenarios (Figure 1b, d) there was a significant narrowing in the range of CI at SS, especially for drugs with higher accumulation.

The proportions of replicates that fail the bioequivalence criteria for CMAX are shown in Figures 2–5. Since these results for scenario I are essentially the same for scenario II, only the results for scenario II are displayed along with those for scenario III. Multiple dose studies had a much higher probability of not failing, particularly if the drug exhibited significant accumulation. For example, the situation described as C2 R2 (high intra-subject variability and high correlation in ka's) combined with high accumulation (A2) and low ka ratio (K2) yields a failure rate of 31% for a SD design but a 3.2% failure rate for the MD design. For a similar situation but with minimal accumulation (A1), the change is from 31% to 11%. A similar pattern was observed when no intra-subject variability (scenario II) was introduced into CL and V (Figure 3).

An even more dramatic effect was observed when the difference in mean ka values was large (K1) as shown in Figure 4 and 5. For the same design C2 R2, the probability of failure for CMAX was 100% in the single dose study. This probability was reduced to only 96.4% in SS condition with minimal accumulation (Figure 4), but when the accumulation index was increased to 2, the probability of failure was reduced to merely 3.7%.

Table III. Estimates of CMAX and their standard error, 90% confidence interval for indomethacin, nifedpine, erythromycin, quindine, and procainamide

		SD				MD					
		CMAX	ESTIMATE	SEE	CI	CMAX	ESTIMATE	SEE	CI	τ	AI
Indomethacin	R	2.03*	−.011	0.148	86–112	1.71*	0.203	0.121	99–123	24	1.03
	T	2.02*				1.94*					
Nifedipine	R	131.1†	−8.91	10.91	79–108	88.21†	3.97	7.43	89–119	6	1.16
	T	122.2†				90.82†					
Erythromycin	R	1.05*	−0.12	0.093	73–103	1.35*	−.106	0.089	80–103	6	1.22
	T	0.92*				1.28*					
Quinidine	R	601.4†	−146.8	39.02	64–86	1224†	−100.7	39.71	85–97	12	1.54
	T	465.2†				1107†					
Procainamide	R	0.96*	0.224	0.053	113–132	2.07*	−.005	0.059	95–105	6	1.76
	T	1.2*				2.07*					

CMAX: peak concentration (*μg or †ng/ml), ESTIMATE: least square difference between test and reference, SEE: Standard error of the ESTIMATE, CI: The confidence interval, τ: Dosing interval, AI: Accumulation Index calculated as $1/(1 - e^{-k\tau})$, SD: Single dose, MD: Multiple dose, R: Reference, T: Test.

Table IV. Estimates of AUC and their standard error, 90% confidence interval for indomethacin, nifedpine, erythromycin, quindine, and procainamide

		SD				MD			
		AUC	ESTIMATE	SEE	CI	AUC	ESTIMATE	SEE	CI
Indomethacin	R	11.35*	−0.046	0.434	93–106	9.93*	0.124	0.433	94–109
	T	11.30*				10.26*			
Nifedipine	R	202†	−.607	9.04	92–108	171.5†	−8.55	8.8	87–104
	T	201.4†				165.3†			
Erythromycin	R	2.77*	−0.033	0.183	88–110	3.62*	−0.104	0.23	86–108
	T	2.69*				3.52*			
Quinidine	R	10073†	−2421	754	63–89	11200†	−1433	376	82–93
	T	7994†				9602†			
Procainamide	R	9.04*	0.049	0.266	96–106	10.24*	−0.008	0.219	96–104
	T	9.10*				10.23*			

AUC: area under the curve (*μg- or †ng-hr/ml), ESTIMATE: least square difference between test and reference, SEE: Standard error of the ESTIMATE, CI: The confidence interval, τ: Dosing interval, SD: Single dose, MD: Multiple dose, R: Reference, T: Test.

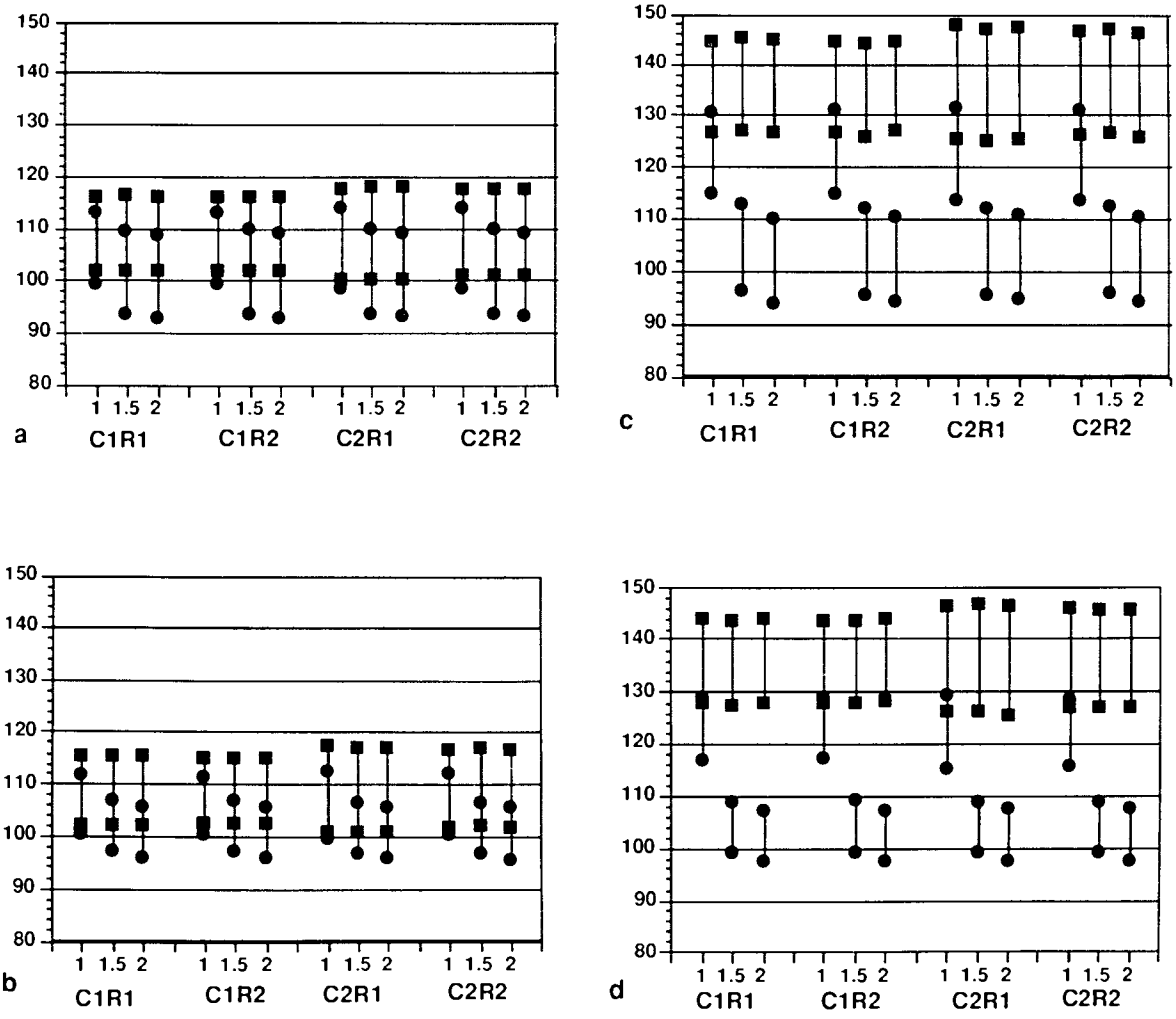

Figure 1. Mean upper and lower confidence intervals (N = 1000) of CMAX for different designs and scenarios under single dose (box) and multiple dose (circle) studies. Figure 1a represents a condition where intra- and inter-individual variability in CL and V was assumed. Figure 1b represents a conditions where only inter-individual variability in CL and V was assumed. For figure 1a, b, ka (test/ref.) = 0.375/0.28. Figures 1c, d represents the corresponding conditions except ka (test/ref.) = 0.375/0.15. The vertical axis is the CI and the horizontal axis represents different degrees of AI under different combinations of CV and R (Appendix I).

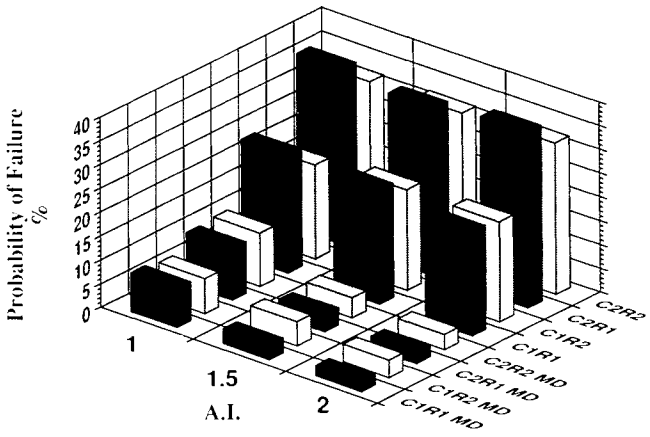

Figure 2. Probability of failing the bioequivalence test for Cmax in scenario III where intra- and intersubject variability in CL and V was assumed; and ka (test/ref.) = 0.375/0.28.

Comparison of scenario II (no intra-subject variability in CL and V) with scenario III (Figure 2 Vs 3) illustrates the importance of intra-subject variability in disposition in bioequivalence assessment when the difference in ka values was not large (Figure 2 Vs Figure 3). The failure ratio was increased when there was intra-subject variation in CL and V (Figure 2) versus when there was not (Figure 3).

For AUC, the failure rate was very low, generally less than 5%, as expected because the simulation included no difference in F between products. However, even at this low failure rate, the pattern across scenarios and designs were similar to those for CMAX. Failures of AUC was mainly observed in scenario III (1–5%). The low failure rate was a reflection of the influence of the intra-individual variability in CL and V on AUC CI.

The sensitivity of "probability of failure" to the ka ratio was evaluated using additional bioequivalence simulations representing a series of ka (test/reference) ratios ranging from 1.1 to 2.5 (Figure 6). A single design described as C1R1A1.CLI (low intra-subject variability and low correlation in ka combined with minimal accumulation and presence of inter- and intra-subject variability in CL and V) was used for these simulations. Ideally, the probability of failure

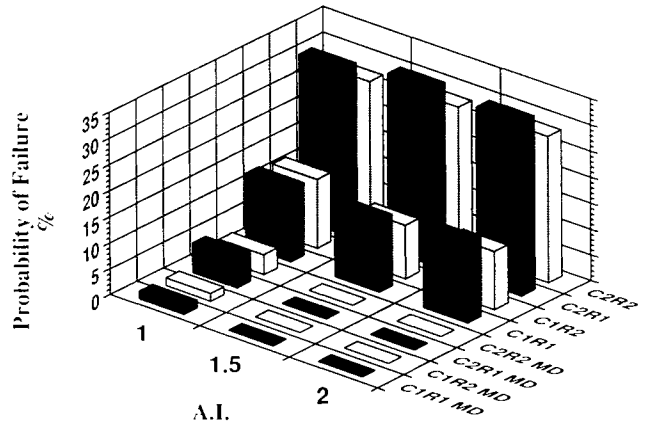

Figure 3. Probability of failing the bioequivalence test for Cmax in scenario II where only intersubject variability in CL and V was assumed; and ka (test/ref.) = 0.375/0.28.

would be zero if the true ratio of ka's is 1.2 or less and 100% if the ratio is greater than 1.2. Obviously this cannot occur in reality. The power curve (Figure 6) demonstrates the greater sensitivity of CMAX based on single dose studies relative to CMAX based on multiple dose studies even when accumulation is minimal. For example, when the ka ratio is 1.5 there is a 30% probability of failure with MD design versus an 80% probability of failure for the single dose study. The power analysis thus reveals the limitations and the relative performance of CMAX as a measure of rate of absorption under SS and non-SS conditions.

DISCUSSION

The results from the ten bioequivalence clinical trials show that AUC is a consistent estimator for the extent of absorption between single and multiple dose studies (Table IV). The simulated data and their analysis (not presented) were in accordance with the results obtained from the clinical data. The CI of AUC was resistant to changes in range or central tendency upon multiple dosing, or upon changes in ka, CV, and correlation. The most noticeable change was the symmetric narrowing of CI for AUC in scenario II upon multiple dosing. Compared to scenario I, where we assumed no variability in elimination, intra- and inter-individual variability in CL and V (scenario III) cause an increase in CI of the AUC for both single and multiple dose studies. Inclusion of inter-individual variability (scenario II) causes an increase in the CI of AUC for single dose studies only.

The proper design and execution of multiple dose studies is far more critical for CMAX. The width of the 90 per cent CI calculated for quinidine and procainamide, both with an AI > 1.5, decreased by almost 50% upon multiple dosing; and consequently, the multiple dose studies passed the bioequivalence test after the single dose study failed it previously (Table III). It is apparent that the estimates of CMAX and their standard errors may differ between single dose and multiple dose studies. Thus, inequivalence of CMAX values for a single dose study does not imply inequivalence for multiple dose study. On the other hand, it can be suggested that multiple dose studies diminish the ability to detect inequivalence in rate of absorption as measured by CMAX.

The simulation studies clearly showed that CI for CMAX was very sensitive and responsive to the various changes in the variables and the pharmacokinetic parameters introduced into the system.

First, similar shift patterns of the CI were observed upon multiple dosing for the three scenarios. These shifts toward the desired region of the acceptance interval could be explained through the consistent decrease of the difference in CMAX at steady-state. Although, the shift was observed with minimal accumulation, it was clear that, the greater the accumulation, the greater the shift. The central tendencies of the CI for CMAX were almost the same for drug products that accumulate regardless of their difference of ka ratios. On the other hand, narrowing of the CI for CMAX could be attributed to the decrease of the standard error of the estimates (SEE) for the difference in CMAX.

Second; in scenarios I and II, the shift of CMAX CI upon multiple dosing was always accompanied with a narrowing of the CI. That narrowing was a consistent response

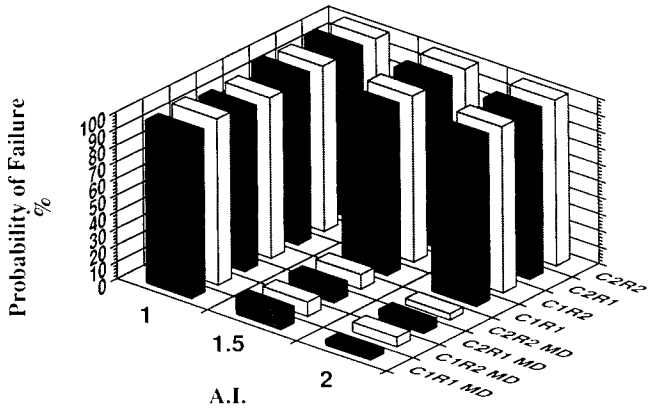

Figure 4. Probability of failing the bioequivalence test for Cmax in scenario III where intra- and intersubject variability in CL and V was assumed; and ka (test/ref.) = 0.375/0.15.

to the increase of the AI. Results from scenario III suggest that in clinical trials of drugs characterized with even modest intra-individual variability in disposition parameters, there is no narrowing but rather a shift in CI upon multiple dosing. This observation reflects the influence of the intra-individual variability on CMAX CI.

It is apparent that CMAX for single dose studies only yields an indirect comparison of ka values. When ka (test/reference) ratio was changed from 1.3 to 2.5, the chances of failing CMAX increased from about 25% to almost 100% (Figure 6). Differences in CMAX on multiple dosing, provided no or minimal accumulation, do not reflect differences in ka until the differences in ka are large. This can be explained by the fact that for drugs that accumulate the CMAX value is composed of both drug from the current dose as well as drug from the previous doses.

Both the shift and narrowing of the CI are reflected in the changes of the probability of passing or failing the bioequivalence test. The most dramatic changes in that probability are seen for drug products that have a big difference in ka and accumulate on multiple dosing. It is the combined effect of narrowing and shift in CI that causes the dramatic decrease in the probability of failing the bioequivalence test.

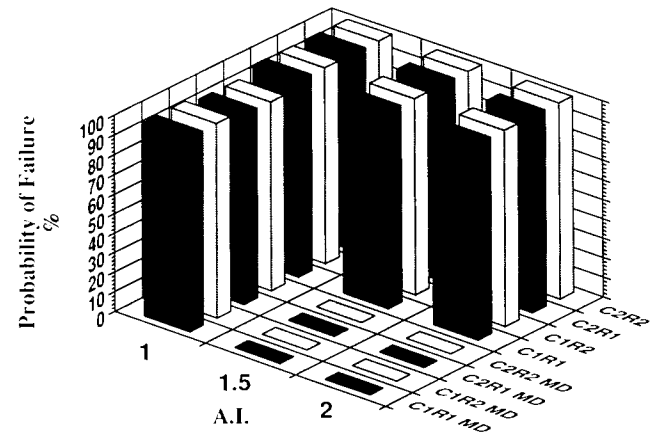

Figure 5. Probability of failing the bioequivalence test for Cmax in scenario II where only intersubject variability in CL and V was assumed; and ka (test/ref.) = 0.375/0.15.

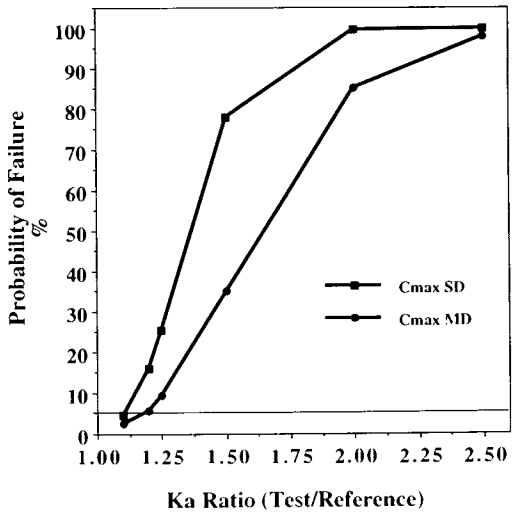

Figure 6. Probability of failure of Cmax for single and multiple dose studies as a function of ka ratio. Scenario III was assumed, where intra- and interindividual variability in CL and V was assumed, a specific design KxC1R1A1.CLI (low intra-subject variation and low correlation for ka's and minimal accumulation) was used with different ka ratios of (test/ref.). At each ka ratio value, the bioequivalence trails were repeated 1000 times.

That effect was so powerful that it dissimulated the effect of the simulation variables along with the effect of the presence or absence of intra- and inter-subject variability in disposition.

APPENDIX I

Symbols and Abbreviations

C1: 25% coefficient of variation in bivariate absorption constants (ka).
C2: 50% coefficient of variation in bivariate absorption constants (ka).
R1: 0.25 correlation coefficient in bivariate absorption constants (ka).
R2: 0.50 correlation coefficient in bivariate absorption constants (ka).
A1: accumulation index of 1.05. (calculated for τ = 36h, $t_{1/2}$ = 8h).
A15: accumulation index of 1.55. (calculated for τ = 12h, $t_{1/2}$ = 8h).
A2: accumulation index of 2.0. (calculated for τ = 8h, $t_{1/2}$ = 8h).
K1: ratio of absorption constant of test/reference = 0.375/0.15.
K2: ratio of absorption constant of test/reference = 0.375/0.28.
CLI: scenario in which inter and intraindividual variability in CL and V are introduced.
CL: scenario in which interindividual variability in CL and V is introduced.
Y: scenario in which there is no variability in CL or V.

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