Absorption Rate Vs. Exposure: Which Is More Useful for Bioequivalence Testing?

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Purpose. The goals were to evaluate the usefulness of C_{max}/AUC_{lqc}, ratio of the maximum plasma drug concentration to the area under the plasma concentration-time curve to the time of the last quantifiable concentration, in bioequivalence testing and to explore the use of exposure as a replacement for the concepts of rate and extent of drug absorption.

Methods. The bioequivalence of products differing in both rate (ka) and extent (F) of absorption was assessed under conditions similar to those encountered in a typical trial. A one-compartment model drug with first-order absorption (rate constant = ka) and elimination was used. Variability was introduced in all model parameters using Monte Carlo techniques. The results were expressed in terms of the probability of declaring bioequivalence in a cross-over trial with 24 subjects using C_{max}/AUC_{lqc}, AUC_{lqc}, and C_{max} as bioequivalence measures.

Results. The outcome of a bioequivalence trial was shown to depend on the measure. C_{max}/AUC_{lqc} reflected changes in ka, but not in F. AUC_{lqc} showed dependence on F, but virtually no dependence on ka. For C_{max}, a 3- to 4-fold increase in ka and a concomittant 20% decrease in F, as well as corresponding changes in the opposite directions, resulted in bioequivalent outcomes.

Conclusions. It was concluded that use of C_{max}/AUC_{lqc} should be discouraged and that defining bioequivalence in terms of rate and extent of absorption has major problems. The goal of bioequivalence trials should be to assure that the shape of the concentration-time curve of the test product is sufficiently similar to that of the reference product. To this end, the use of "exposure" rather than "rate and extent of absorption" concepts is encouraged.

KEY WORDS: absorption rate; bioequivalence; C_{max}/AUC_{lqc}; C_{max}/AUC; exposure.

INTRODUCTION

"Rate of absorption" is the nemesis of bioequivalence testing. Not everyone agrees on what it is and, even when they do, no one can find an appropriate measure of it. The problem with absorption rate arises from the way in which bioequivalence is defined in the United States Food, Drug, and Cosmetic Act (section 505(j)(7)(B)). As defined in the Act, bioequivalence is declared if the rate and extent of absorption of the drug in test and reference formulations do not show significant differences when the drug is administered at the same molar dose under similar experimental conditions in either a single dose or multiple doses. Rate is allowed to be different if the difference is intentional, reflected in labeling, not essential to the attainment of effective concentrations on chronic use, and considered unimportant to therapeutic outcome. The United States Food and Drug Administration is given the responsibility to determine how rate and extent are to be assessed and to set standards for what is meant by "significant differences", "same", and "similar". The underlying principle is that products should be therapeutically equivalent if the drug (or active metabolite or both) shows bioequivalence. The rate and extent measures thus become surrogate indicators of therapeutic outcome or, at the least, markers to assess drug product performance.

Considerable time and effort has been spent to find a universal measure of absorption rate (1–10). The maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) are thought to be reasonable measures of it (1,4–6). However, C_{max} depends on extent of absorption and, for this reason, is often not a reliable rate measure (7). Furthermore, C_{max} has been shown to be relatively insensitive to changes in absorption rate (4,11). The measure t_{max} has been found to be a relatively sensitive measure of absorption rate (1), but often fails because it is a discrete measure that depends on frequency of blood sampling and, in the case of minimally varying concentrations near the peak, on assay reproducibility.

Why is a rate measure so difficult to find? The answer lies in Fig. 1. Rate is not a single number; it varies with time. As shown, the rate-time profiles may differ greatly even when the mean absorption time is the same (0.72 hr). First-order, zero-order and bolus inputs are shown. The rate-time profile typically observed is undoubtedly more complex because of

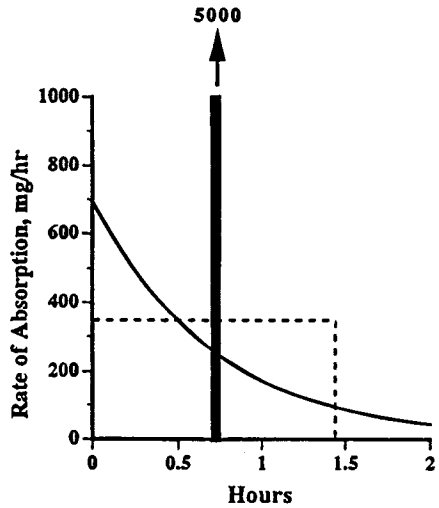

Fig. 1. Rate of absorption varies with time; no single measure of it is possible. Shown are the rate-time profiles of three situations in which the mean absorption time is the same, 0.72 hr. Absorption follows first-order (solid line), zero-order (short dashed line) and bolus (heavy solid line) characteristics following the administration of 500 mg. The first-order rate constant is 1.39 hr^{-1}; the zero-order rate is 347 mg/hr. As shown, the bolus is given over 6 minutes.

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the interactions of many pharmaceutic and physiologic factors. Using a single measure to assess rate is analogous to using a single concentration to represent the entire concentration-time profile. To obtain information on the absorption rate-time profile from the typical plasma concentration-time profile requires modeling, deconvolution, and a number of assumptions. Thus, rate information is difficult to acquire and is often imprecise.

One rate measure that has received special attention recently in bioequivalence testing (3–5,7,8,11) is C_{max}/AUC, ratio of the maximum plasma concentration (C_{max}) to the area under the plasma concentration-time curve (AUC). Tothfalusi and Endrenyi (11) recently observed that C_{max}/AUC_{lqc}, ratio of C_{max} to the area under the plasma concentration-time curve to the last measurable concentration (AUC_{lqc}), is a more reliable rate measure than C_{max}/AUC in situations in which the area beyond the time of the last measurable concentration has a large error (e.g., when disposition is multiexponential). C_{max}/AUC_{lqc} has the property of being essentially independent of changes in extent of absorption and has been shown to be a more specific measure of rate than C_{max}.

This paper focuses on two issues. The first is the usefulness of C_{max}/AUC_{lqc} in bioequivalence testing. The second is whether a measure of absorption rate should even be sought. The later issue was the subject of a recent paper by Rostami-Hodjegan *et. al.* (12).

METHODS

The behavior of C_{max}/AUC_{lqc} as a rate measure was examined by simulation. Products differing in both rate (rate constant, ka) and extent (F) of absorption were evaluated. Variability typically encountered in humans was introduced into model parameters using Monte Carlo methods. Details are given in a previous report (2). The following is a brief summary. In all cases, data sets of 1540 bioequivalence clinical trials were generated. Each trial consisted of a cross-over design with 24 subjects and two formulations.

The pharmacokinetic models and parameter distributions used were set according to scenarios that reflect situations commonly encountered in bioequivalence testing (2). In the simulations reported here, the scenario for the reference formulation after oral administration was; a one-compartment distribution model with mean first-order absorption and elimination rate constants of 1.39 hr^{-1} and 0.347 hr^{-1}, respectively, and no lag-time. For all studies, an arbitrary single oral dose of 500 mg was used.

From population distributions, a set of pharmacokinetic parameter values was sampled for each subject. At each trial period, intra-individual variability was added to the subject's baseline values, forming new parameter values. These values were assumed to remain constant throughout a trial period. Two periods, during which each formulation was administered, were simulated. Differences between the two formulations were introduced by changing the mean values of both the rate (ka) and extent (F) of absorption. Assay error was added to the plasma drug concentrations simulated by the model. Variabilities were taken to be the same for the two formulations and no period effects were introduced.

Individual plasma concentrations were simulated using specific inter-individual and intra-individual distributions for each parameter. Analytical assay errors were generated from truncated normal distributions with mean zero and a standard deviation equal to 10% of the mean + LQC, where LQC is the lowest quantifiable concentration. LQC was 1% of the peak concentration of the reference product. Below this limit, the coefficient of variation of the assay was greater than 20%.

In this study, the behavior of three measures, namely, C_{max}/AUC_{lqc}, AUC_{lqc}, and C_{max} were examined. AUC_{lqc} was computed by the trapezoidal method. C_{max} was the highest observed concentration in each individual. C_{max}/AUC_{lqc} was simply the ratio of the two separate measures in each individual subject. The probability of declaring bioequivalence (90% confidence interval for the ratio of averages falling completely within the limits of 0.8 and 1.25) (13) was examined in the presence of actual differences between test and references products.

RESULTS AND DISCUSSION

Power of Measures to Declare Bioequivalence

In the presence of variability in both kinetics and assay, the behavior of C_{max}/AUC_{lqc} reflects differences in ka, but not in F. This behavior is shown in Fig. 2A in which systematic differences between the formulations in both F and ka are introduced in the simulations. The figure shows the power of C_{max}/AUC_{lqc} to declare bioequivalence in the presence of differences in ka, as expressed by the ratio of ka values of test and reference formulations. The probability of not declaring bioequivalence when indeed the products are equivalent is a *producer risk.* For a test product that actually falls outside the 0.8 and 1.25 limits (not bioequivalent), the probability of declaring bioequivalence in the study is a *consumer risk.* C_{max}/AUC_{lqc} better reflects differences in ka than in F, although the range of the F ratio tested is only 0.75–1.25. The measure is not sensitive, however, to changes in ka, as ka of the test product can be 250 to 300% larger than that of the reference product and still show more than a 5% probability of declaring bioequivalence. The principal question is whether such differences in rate (ka) are therapeutically relevant. The use of 80% to 125% for the regulatory window for C_{max}/AUC_{lqc} implies that large differences in ka are acceptable. Thus, ka would appear to have relatively little clinical relevance. Furthermore, detectable differences in rate for a given measure vary with the pharmacokinetic scenario or drug (14). Different regulatory requirements may be needed, depending on the pharmacokinetics of the drug. In this context, the purpose of using C_{max}/AUC_{lqc} as a rate measure is unclear.

The behaviors of AUC_{lqc} and C_{max} differ substantially from that of C_{max}/AUC_{lqc}. AUC_{lqc} in the scenario evaluated has virtually no information on changes in ka, but does show sensitivity to changes in F (Fig. 2B). There is approximately a 5% probability of declaring bioequivalence with this extent measure when the F ratio is either 0.8 or 1.25. The producer risk is correspondingly low for products identical in F. C_{max}, affected by changes in F and, to some degree, ka, shows complex behavior with respect to the probability of declaring bioequivalence with changes in absorption (Fig. 2C). A conclusion of bioequivalence with this measure and AUC_{lqc} is possible if ka is 4 times larger than that of the reference formulation and the F ratio approaches 0.8. A similar conclusion is also possible if the ka ratio is 0.5 and the F ratio approaches 1.25. C_{max} shows

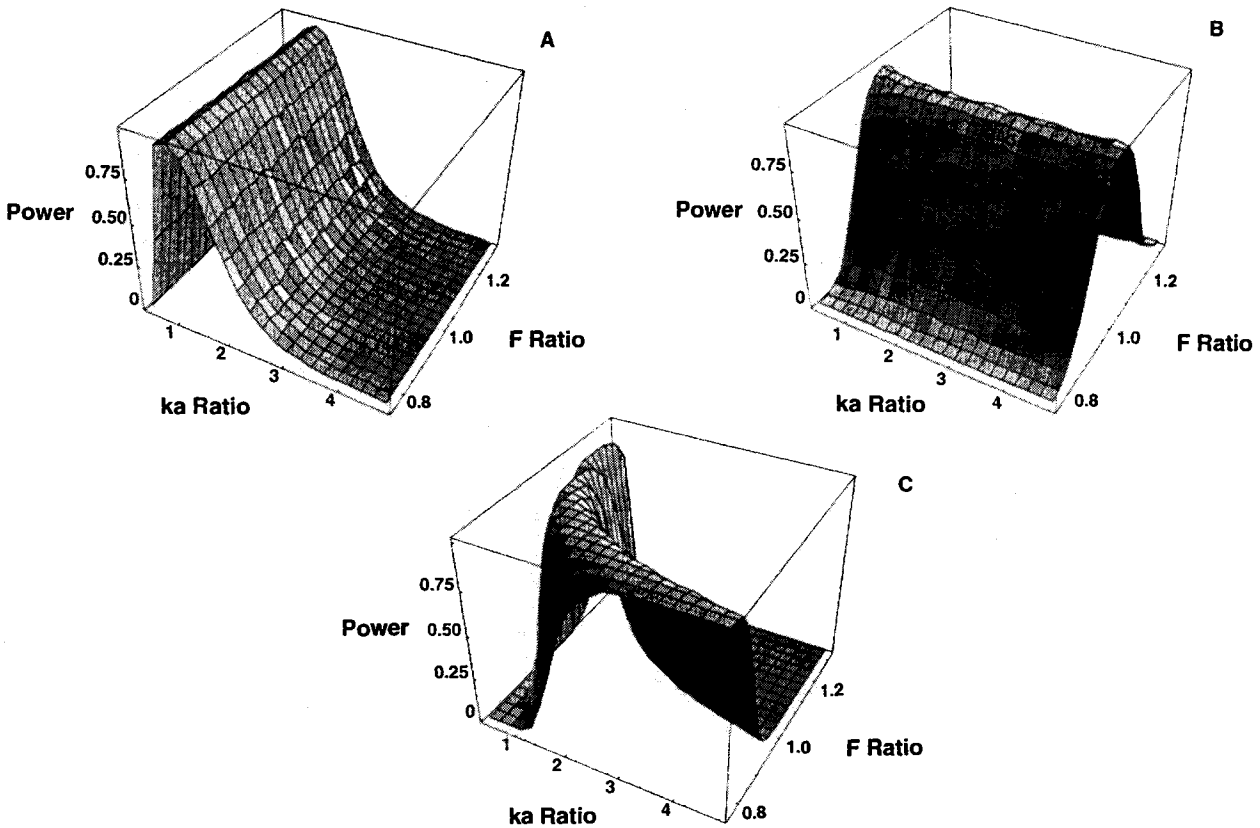

Fig. 2. In the presence of differences in ka and F: A. C_{max}/AUC_{lqc} shows a high probability of declaring bioequivalence (power) when the ka ratio is near one regardless of the F ratio of the test and reference products. The probability remains relatively high even at ka ratios that deviate from 1 by a factor of 2 or more. B. AUClqc clearly reflects differences in F, but not in ka. C. C_{max} reflects differences in both ka and F and, in the scenario evaluated, is much more sensitive to changes in F than in ka (note the differences in the ka and F scales).

greater sensitivity to F than to ka, but the power of the measure clearly depends on both ka and F. Under the conditions tested, C_{max}/AUC_{lqc} appears to be a more specific measure than C_{max} in reflecting changes in ka. Like C_{max}, however, the measure is not sensitive to changes in ka. Both measures may indicate bioequivalence by the current regulatory requirements even if ka values of the test and reference formulations differ 2- to 3-fold. When F is reduced, the rate-time profile is correspondingly reduced for the same value of ka. Thus, no change in ka does not mean the rate of absorption is not changed. In this sense, C_{max} tends to better reflect changes in rate than ka.

One can envisage scenarios in which both C_{max}/AUC_{lqc} and AUC_{lqc} are greater for the test formulation than for the reference formulation leading to a much higher C_{max} value for the test product. In the limit, C_{max} may be 56% higher for the test product if the test/reference ratio of the means is 1.25 for both C_{max}/AUC_{lqc} and AUC_{lqc}. Conversely, it is possible that both AUC_{lqc} and C_{max}/AUC_{lqc} are smaller for the test formulation than for the reference formulation. C_{max} values 36% lower for the test product than for the test product result if the test/reference ratio is 0.8 for both C_{max}/AUC_{lqc} and AUC_{lqc}. Thus, a product may pass the criteria for both C_{max}/AUC_{lqc} and AUC_{lqc}, but the test product may be therapeutically inequivalent if the C_{max} value, a measure of peak exposure, reflects drug activity. The information gained from measuring C_{max}/AUC_{lqc} may have much less therapeutic relevance than that from C_{max} particularly with respect to the safety of the drug product.

Another feature of C_{max}/AUC_{lqc} is that it is the ratio of two measures that correlate strongly with the amount absorbed. C_{max} and AUC_{lqc} tend to covary because of their mutual dependence on F. Thus, the variability of the ratio is expected to be less than that of either measure alone. Bioequivalence might thus be declared even under circumstances in which a lack of bioequivalence is shown using C_{max}, which raises safety concerns.

Overall, the C_{max}/AUC_{lqc} measure provides some information on absorption rate, but it is not sensitive to changes in the absorption rate constant. It may allow declaration of bioequivalence more readily because both C_{max} and AUC_{lqc} correlate with F, and the variability of the C_{max}/AUC_{lqc} measure is reduced compared with C_{max}. However, as illustrated above, even when equivalence can be shown with both AUC_{lqc} and C_{max}/AUC_{lqc}, the C_{max} values may not be equivalent between formulations. Despite the contention that Cmax is not a good parameter for the estimation of rate of absorption, it does provide a measure of peak exposure which may relate to the safety and efficacy of a drug product clinically. Therefore, the use of C_{max}/AUC_{lqc} should be discouraged in bioequivalence testing.

Exposure Concept

The general objective of bioequivalence testing is to assure that the internal exposure to the drug is sufficiently similar for both formulations. We might consider systemic exposure as

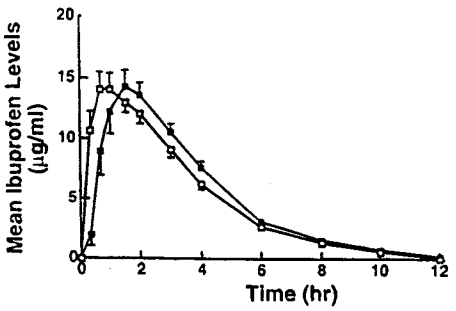

Fig. 3. Test (■) and reference (□) 200-mg formulations of ibuprofen have been shown (10) to have the same total and peak exposures, but different early exposures. As onset of action is important to analgesic therapy with this drug, it is apparent that bioequivalence testing of such drug products should include a measure of early exposure.

having three major underlying characteristics. The first is *total* exposure to the drug. Total exposure is readily assessed by AUC_{tqc}. *Peak* exposure is a second characteristic of potential concern for safety reasons. C_{max}, a measure of this property, can sometimes be highly variable. Abandoning C_{max} because of its high variability seems inappropriate when no other measure of peak exposure is available. In the presence of high variability, consideration might be given to widening the acceptance window, e.g., to 70/143 as used in Europe for the 90% confidence interval, or to the use of the average of the two or three highest concentrations. Measurement of C_{max} is particularly appropriate for drugs that show a toxic effect closely related to the plasma concentration (e.g., hypotensive effects). A third characteristic of occasional therapeutic importance is *early* exposure. Such occurs when a quick onset of action is needed. Here bioequivalence implies comparable exposures at early times. Figure 3 shows the concentration-time profiles of two formulations of ibuprofen with the same total and peak exposures but different early exposures (10). As this drug is used to treat a headache, the products may not be therapeutically equivalent even though their C_{max} and AUC (and C_{max}/AUC_{tqc}) values are similar.

The question of how to assess early exposure is beyond the scope of this paper. Partial area under the curve has been proposed (4,10) as such a measure. It has been demonstrated (4) that partial area to t_{max} of the reference product (AUCp) is a sensitive measure for rate from both kinetic and statistical considerations. A high producer risk is a concern for this measure, however, when a variable lag time is present (4). Under such circumstances, it is extremely difficult to demonstrate bioequivalence using the 90% confidence interval criteria of 80–125% because of the large variability typically observed in rate-time profiles. In such cases, AUCp could be assigned a different equivalence interval. Another alternative is to use a partial area up to some time after the reference t_{max} (3). It is noteworthy that AUCp has been employed by the Canadian regulatory agency (17) as an additional parameter for assessment of bioequivalence of drugs for which an early onset or rapid rate of absorption is considered important. The primary purpose of the exposure concept is to encourage movement away from the "rate and extent of absorption" way of thinking. The measures of exposure may be similar to those currently used, but the exposure concept redirects our thinking and encourages us to focus on the shape of the concentration-time curve.

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