Pharmaceutical Research, Vol. 14, No. 8, 1997

Commentary

C_{max}/AUC, A Commentary

Thomas N. Tozer[1,3] and Walter W. Hauck[2]

Received April 8, 1997; accepted May 15, 1997

KEY WORDS: secondary metrics; C_{max}; C_{max}/AUC; bioequivalence.

Endrenyi and Tothfalusi (1) recently presented arguments for the use of secondary metrics in bioequivalence testing. We agree that measures, other than AUC, may be useful in such testing. We also agree that the other metrics should yield information additional to AUC. We differ, however, in our view of the utility of C_{max}/AUC and wish to express it.

The raison d'être of bioequivalence testing is to ensure that a test product is therapeutically equivalent to a reference product. The bioequivalence trial involves assessment of the pharmaceutical and pharmacokinetic equivalence of the products. Emphasis is placed on the latter based on the concept that products are therapeutically equivalent if rate and extent of absorption of the active compound (drug and/or metabolite) are sufficiently similar.

AUC is universally accepted as a measure of the extent of drug absorption. In most therapeutic situations, assurance of a similar extent of absorption in the test and reference products is essential. For many drugs, or for a few in specific indications, the rate-time profile of drug absorption becomes relevant. This is especially true for onset of action, for occurrence of adverse effects, or for over-extension of the pharmacologic response (2). Many absorption-rate versus time profiles may be consistent with a given value of C_{max} or C_{max}/AUC. Thus, neither metric assures similarity in onset of action as would be the case for similar initial rate-time profiles. C_{max}, however, offers some advantage as a measure of the potential for adverse effects or an unreasonable extension of its pharmacologic effects, both safety issues.

Endrenyi and Tothfalusi (1) state that the principal merit of C_{max}/AUC as a secondary metric is its enhanced specificity (less dependence on variation in the extent of absorption). We do not disagree that it may more specifically reflect differences in rate of absorption than C_{max}, but it may contain little information of therapeutic value and may indeed be misleading. Consider situations in which C_{max} relates to drug safety. If the bioequivalence goal posts are set at 0.8 and 1.25, as they are for C_{max}/AUC, then the implied goal posts for C_{max} are 0.640 and 1.563. The wider window for C_{max} occurs because bioequivalence can be declared when both AUC and C_{max}/AUC are increased by a factor of 1.25 or decreased by a factor of 0.8.

Even if one concludes that a metric for rate is needed and that C_{max}/AUC is a better metric for rate than C_{max}, a further problem exists. Any fixed goal post for C_{max}/AUC (or for C_{max}) corresponds to a variable goal post for rate of absorption as, for example, reflected by a first-order absorption rate constant. The goal post for rate depends on the pharmacokinetic scenario, particularly with respect to the sensitivity of the metric to changes in rate and to the sources of variability (3). If one, conversely, fixed the goal posts for rate (rate constant), one would need to know the pharmacokinetic scenario in order to determine the goal post for C_{max}/AUC. An advantage to C_{max} is that it has interpretive value, independent of rate, namely as a measure of safety. Accordingly, goal posts can be set for C_{max} without reference to the goal posts being set for rate.

We also agree that C_{max}/AUC often has less variance than C_{max}. Therefore, products are more likely to meet the current FDA requirements for the 90% confidence interval to remain within the 0.8–1.25 window with this measure than with C_{max}. This may not always be the case, however. We see this empirically in the data presented by Elze et al., (4) for which C_{max}/AUC had a higher coefficient of variation (CV) than C_{max} in 22% of the studies. The variance of C_{max}/AUC depends on the correlation of C_{max} with AUC. If totally independent of each other, the CV of the ratio is expected to be greater than the CV of either measure alone. There would be no advantage here to the use of C_{max}/AUC over C_{max}. At the other extreme, if the correlation coefficient approaches 1.0, there again is no advantage to C_{max}/AUC as the ratio has no information additional to that of AUC. Indeed, only for correlation coefficients between roughly 0.5 and 0.9 is there both a decrease in CV and availability of additional information. However, as discussed above, the additional information is not necessarily therapeutically relevant. Thus, any argument for C_{max}/AUC has to be based on its interpretability and clinical usefulness, rather than on its statistical properties.

In our view, C_{max} is the preferred metric. If the reference product shows variability in C_{max} comparable to or greater than that of the test product, thought should be given to widening the goal posts, based on the variability of the reference product. This is the case in individual bioequivalence (4). Of overriding importance, however, is the usefulness of the measure to therapy with the drug. Using a measure simply to lower variability and

[1] Department of Biopharmaceutical Sciences, School of Pharmacy, University of California, San Francisco, California 94143-0446.

[2] Division of Clinical Pharmacology, Thomas Jefferson University, 125 South 9th St., Sheridan Bldg., Suite 403, Philadelphia, Pennsylvania 19107.

[3] To whom correspondence should be addressed. (e-mail: Tntozer @aol.com)

0724-8741/97/0800-0967$12.50/0

pass bioequivalence test criteria without considering therapeutic consequence is inappropriate.

ACKNOWLEDGMENTS

We thank Martina Elze for providing data from reference 4.

REFERENCES

1. L. Endrenyi and L. Tothfalusi. Secondary Metrics. *J. Pharm. Sci.* **86**:401–402 (1997).
2. T. N. Tozer, F. Y. Bois, W. W. Hauck, M.-L. Chen, and R. L. Williams. Absorption rate vs. exposure: which is more useful for bioequivalence testing? *Pharm Res.* **13**:453–456 (1996).
3. F. Y. Bois, T. N. Tozer, W. W. Hauck, M.-L. Chen, R. Patnaik, and R. L. Williams. Bioequivalence: Performance of several measures of rate of absorption. *Pharm Res.* **11**:966–974 (1994).
4. M. Elze, H. Potthast, and H.H. Blume. Metrics of absorption. Data base analysis. In *Bio-International 2, bioavailability, Bioequivalence and Pharmacokinetic Studies*, H. H. Blume, and K. K. Midha, eds, Stuttgart, 1995, pp. 61–71.