Determination of the Area Under a Curve

In a recent article, Tai (1) describes a method to determine total area under metabolic curves. However, what is exaggerately called "Tai's mathematical model" is nothing but a simple geometrical formula, well known for many years as the trapezoidal rule. This classical method, as well as a series of other approaches, was reviewed and investigated by Wagner and Ayres (2) 17 years ago. Moreover, the derivation of the trapezoidal rule is presented in a circumstantial way, the final equation called "Tai's formula" contains incorrect notations (e.g., 'x' must be 'X' with the author's definitions), and the division into different conditions of intercept and passing the origin is absolutely unnecessary.

The validation of the formula by means of comparison with a "true value" is useless and contains several fallacies. First, because of the geometrical interpretation of the trapezoidal rule, it is clear that the expression tends toward the true area under the curve (AUC) if the number of considered curve points increases. Hence, the adequacy of the trapezoidal rule is dependent on the number of curve points and cannot be investigated by a few examples. Second, the AUC value measured graphically by counting the numbers of small units under the curve is not the true AUC value. Like the trapezoidal rule, it is an approximation, which tends toward the true value if the units decrease. Thus, for comparison, not the true but another approximation was used. Third, Student's t tests were misused. Significance tests are generally inadequate tools for comparison of two methods of measurement (3). In addition, the sample size was only $n = 5$, resulting in very low power, and multiple comparisons were made without adjustment. However, even if the sample size had been larger and adjustment for multiple comparisons had been made, in principle, approaches adequate for method comparison should have been used (3).

Finally, the term *total area under a curve* is used in another sense than it is in the pharmacokinetic literature. The word *total* refers to AUC(0-∞), whereas AUC(0-*T*), where *T* is the investigator's last time point, is a partial area. Only the latter can be estimated by means of the trapezoidal rule; computation of the total AUC(0-∞) requires a mathematical or pharmacokinetic model (2). However, "Tai's mathematical model" is no model, it is an application of a simple geometrical rule.

In conclusion, Tai proposed a simple, well-known formula exaggeratedly as her own mathematical model and presented it in a circumstantial and faulty way.

RALF BENDER, PHD

From the Department of Nutrition and Metabolic Diseases, Heinrich-Heine University, Düsseldorf, Germany.

Address correspondence to Ralf Bender, PhD, Department of Nutrition and Metabolic Diseases, Heinrich-Heine University, P.O. Box 10 10 07, D-40001 Düsseldorf, Germany.

References

1. Tai MM: A mathematical model for the determination of total area under glucose tolerance and other metabolic curves. *Diabetes Care* 17:152–154, 1994
2. Wagner JG, Ayres JW: Bioavailability assessment: methods to estimate total area (AUC 0-∞) and total amount excreted (A_e^{∞}) and importance of blood and urine sampling scheme with application to digoxin. *J Pharmacokinet Biopharm* 5:533–557, 1977
3. Altman DG, Bland JM: Measurement in medicine: the analysis of method comparison studies. *Statistician* 32:307–317, 1983

Comments on Tai's Mathematic Model

I commend Tai (1) for producing a correct method for calculating the total area under the curve. It uses the trapezoid rule, a basic geometrical concept, which is that the area of a trapezoid is the mean of the length of the two parallel sides times the width. This method has been used by those of us in the field for many years and, in my opinion, does not need a new name. I also have a number of other problems with her paper. Tai considers that the "true value" for the area under the curve is obtained by plotting the curve on graph paper and counting the squares under the curve. This method is subject to a number of errors arising from inaccuracies in plotting the points and lines and in estimating the area of the portions of squares that are bisected by lines whose width is large in relation to the size of the squares. The trapezoid rule is, in fact, the gold standard for calculating areas if the points are joined by straight lines.

The typographical error in the example calculation (which should read: area = 1/2[30(95 + 147) + 30(147 + 124) + 30(124 + 111) + 30(111 + 101)] = 14400) is a problem I cannot criticize. In one of my papers, there are a number of confusing errors in the section describing the effects of different ways of calculating the area under the curve that I was careless enough not to pick up in proof (2).

However, I will criticize her totally inappropriate use of "my" formula to calculate total area under the curve (3). As was clearly stated, my formula is for calculating the incremental area under the curve above the baseline and does not give the correct value for the total area. Therefore, her comparison of the accuracy of "her" method with "mine" is a completely meaningless exercise. In addition, to obtain the area she ascribes to my method (i.e., 13,517), she must have used the incorrect final term $tD^2/[2(D+|E|)]$, which, as explained, is only