SAS Programming to Calculate AUC in Pharmacokinetic Studies
—Comparison of Four Methods in Concentration Data

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ABSTRACT

AUC is an important parameter in pharmacokinetic studies. There are different ways to calculate AUC. Sometime, the statistician or pharmacokineticist has to choose one particular method to calculate AUC depending on the actual concentration data. Among many pharmacokinetic approaches and modeling analyses, traditional trapezoidal, log-linear trapezoidal, Lagrange polynomial integration, and Purves method are commonly used in calculation of AUC.

This paper will discuss the four methods of AUC calculation in pharmacokinetic studies of drug. SAS will be used in application of those methods. A comparison of the four methods will be presented and analysis of the strength and weakness of these methods based on sample data will be performed. In conclusion, some general comments and suggestions will be provided.

INTRODUCTION

PK (pharmacokinetic) is the kinetics of drug absorption, distribution, and elimination. It studies how the drug is absorbed, distributed and eliminated in the body.

The major measurements of PK study are plasma and urine. So, in most of time the PK study data is plasma concentration data. The AUC (the area under curve) can be presented graphically as the area under the plasma concentration versus time curve. AUC is an important parameter in PK analysis. AUC analysis, often used as a measure of drug exposure, plays many important roles in pharmacokinetics. AUC provides a measure how much and how long a drug stays in a body. There are different ways to calculate AUC. Sometimes, the statistician or pharmacokineticist has to choose one particular method to calculate AUC depending on the actual concentration data.

There are two major different approaches to calculation of AUC: one is compartmental modeling analysis; the other is model independent (non-compartmental) analysis. Among the non-compartmental approach, traditional trapezoidal, log-linear trapezoidal, Lagrange polynomial integration, and Purves method are currently being used.

1) The linear trapezoidal method
The linear trapezoidal method is the most intuitive method of numerical integration of area under the curve. The linear interpolation is presumed between any two adjacent concentration time points. A straight line as \( Y_{i-1} = a + bt_{i-1} \) can be approximated

\[
\int_{t_1}^{t_2} = \frac{h}{2} (y_1 + y_2)
\]

In SAS programming, partial AUC can be calculated as:

\[
\text{AUC}_{\text{partial}} = ((\&C_0 + \&C_1) * (.5)) * (\&T_1 - \&T_0);
\]

\( C_0 \) and \( C_1 \): two adjacent concentration points;
\( T_1 \) and \( T_0 \): two adjacent time points;

Then all partial AUC can be summed up as:

\[
\text{AUC} = \text{sum (AUC}_t, \text{AUC}_{\text{partial}(i-1)})
\]

(AUC\(_t\): AUC at time \( t\))

2) The log-linear trapezoidal method
The log-linear trapezoidal method is based on the assumption that the concentration data is distributed exponentially over the time.

\[ y = y_0 - k \cdot t = \frac{y_2 - y_1}{-k} \]

Upon above assumption, the AUC can be calculated as:

\[
AUC = \int_{t_1}^{t_2} y(t) \, dt = h \cdot \frac{y_2 - y_1}{\ln\left(\frac{y_2}{y_1}\right)}
\]

In SAS programming, partial AUC using log-linear trapezoidal rule can be calculated as:

\[
AUC_{\text{partial}} = \frac{((C_0 + C_1) \cdot (T_1 - T_0))}{\log(C_0) + \log(C_1)}
\]

(C0 and C1 : two adjacent concentration point; T1 and T0 : two adjacent time point)

Then all partial AUC can be summed up as:

\[
AUC = \text{sum}(AUC_t, AUC_{\text{partial}_{(i-1)}})
\]

(AUC_t : AUC at time t)
3) The Lagrange polynomial integration method

The Lagrange method uses a piecewise cubic polynomial rule to approximate the concentration time curvature. A set of four closest data points are used for approximation:

\[ y = a_i + b_i \cdot t + c_i \cdot t^2 + d_i \cdot t^3; \]

The Lagrange AUC can be calculated as:

\[ \int_{t_{i-1}}^{t_i} AUC = a_i(t_i - t_{i-1}) + \frac{1}{2} b_i(t_i^2 - t_{i-1}^2) + \frac{1}{3} c_i(t_i^3 - t_{i-1}^3) + \frac{1}{4} d_i(t_i^4 - t_{i-1}^4) \]

The partial AUC in every four cubic polynomial block can be summed up as: AUC = sum (AUC_t, AUCcubic_(i-1)); (AUC_t: four cubic AUC at time t)

4) The Purves method
The Purves method is a hybrid method combining log-trapezoidal and parabola-through-the-origin methods. It was introduced in detail by Paul B. Laub and James M. Gallo (Journal of Pharmaceutical Sciences, Volume 85, Number 4, April 1996).

Paul B. Laub also developed a window-based computer program to use the Purves method to calculate AUC.

\[ C t^2 + d t \]

In early absorption phase, parabola-through-the-origin will be used, while log-linear method will be used in the elimination phase to calculate AUC.

The linear method can be used alone or in conjunction with log-linear method if concentration data has a smooth "up and down" profile. The linear trapezoidal can be used for both ascending and descending portion of the curve while descending portion is generally concaved by log-linear method. It is generally understood by PK analyzers that the linear method usually underestimates the AUC but overestimates it in descending phase. The Lagrange method can be used to estimate the AUC by interpolating values between consecutive data points for the data with multiple peaks.
FOUR METHODS USED IN PK CONCENTRATION DATA

Let’s apply the four methods above to a sample concentration data of patients receiving a single 100 mg dose of ABC.

A PK concentration data table will be displayed for analysis. The concentration graphs and tables will be constructed using SAS program as the linear trapezoidal and Lagrange integration require the examination of concentration data and selection of data points used in the analysis.

PROTOCOL: ABC
Plasma Concentration of Compound in Patients Receiving A Single Dose 100 MG Dose

| Subject | 0   | 0.25 | 0.5  | 0.75 | 1   | 1.5  | 2    | 3    | 4    | 6    | 8    | 12   |
|---------|-----|------|------|------|-----|------|------|------|------|------|------|------|------|
| 001-002 | 0   | 0.55 | 1.48 | 3.72 | 4.38| 8.4  | 6.43 | 2.07 | 1.03 | 0.2  | 0.12 | 0.04|
| 001-003 | 0   | 0.19 | 1.31 | 2.91 | 4.44| 12.06| 7.86 | 3.15 | 1.82 | 0.43 | 0.2  | 0.07|
| 001-004 | 0   | 0.2  | 0.56 | 0.82 | 0.65| 0.94 | 1.65 | 7.52 | 0.67 | 0.18 | 0.05|
| 001-005 | 0   | 0.23 | 11.39| 10.21| 7.63| 4.21 | 2.38 | 1.48 | 0.9  | 0.24 | 0.12 | 0.03|
| 001-006 | 0   | 0.12 | 10.05| 8.84 | 7.38| 4.18 | 3.14 | 1.05 | 0.48 | 0.13 | 0.06|
| 001-007 | 0   | 1.45 | 2.07 | 3.76 | 3.25| 7.91 | 8.3  | 2.72 | 1.29 | 0.29 | 0.13 | 0.06|
| 001-008 | 0   | 0.11 | 4.25 | 8.35 | 9.35| 5.76 | 9.53 | 3.39 | 0.69 | 0.26 | 0.07|
| MEAN   | 0   | 0.4416| 4.3928| 5.4785| 5.3214| 6.1671| 5.5114| 2.5828| 2.3471| 0.3785| 0.1528| 0.05333|
| STD    | 0   | 0.5196| 4.5082| 3.6232| 2.9443| 3.6772| 3.3319| 1.6555| 2.4683| 0.2255| 0.0655| 0.01632|

Note: Minimum quantifiable concentration is 0.03 mg/L

PROTOCOL: ABC
AUC Calculation Comparison

<table>
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<tr>
<th>Subject</th>
<th>Trapezoidal</th>
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<th>Lagrange</th>
<th>Purves</th>
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</table>
COMPARISON OF FOUR METHODS

The strength of linear trapezoidal method is that there is not any model assumed, and it can be approximated and validated by hand or spread sheet application.

The weakness is that it may underestimate the AUC if the data show the convex curvature; on the other hand, it may overestimate the AUC if the data show the concave curvature. The accuracy of linear trapezoidal rule also depends on the width of time interval. The wider time intervals are, the less accurate the AUC approximation is.

The power of log-linear trapezoidal method is that it is the best method when the concentration data demonstrate a nature of mono-exponential distribution with a decline curvature.

However, log-linear trapezoidal method is not good for any other data distribution that mono-exponential will not fit.

The Lagrange cubic polynomial method has a unique merit of fitting in general plasma concentration data as it approximates a smooth curve around the actual data. According to physiological principle, in general, the concentration level arise and decline gradually as a smooth curve.

But, without looking and correct ill-placed data, the Lagrange cubic polynomial method handles data with sharply changed value poorly.

The advantage of the Purves method is its combination of Lagrange cubic rule and parabola-through-the-origin. It does not require graphical examination and correction of data. At early absorption phase with negative curvature, parabola-through-the-origin approximates the data very well. At later elimination phase with positive curvature, it also approximates the data fairly close.

The disadvantage of Purves is that it requires tedious programming and it does not handle ill-places data well—such as irregular curvature or multiple peaks data.

CONCLUSION

The above four methods can be used upon different PK data scenario. Some methods are good for some conditions, and others are good for the other conditions as described above. A good practice is to always examine the data and adjust your assumption and methods.
The thumb of the rules is that any method chosen should be based on the nature of the data.

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