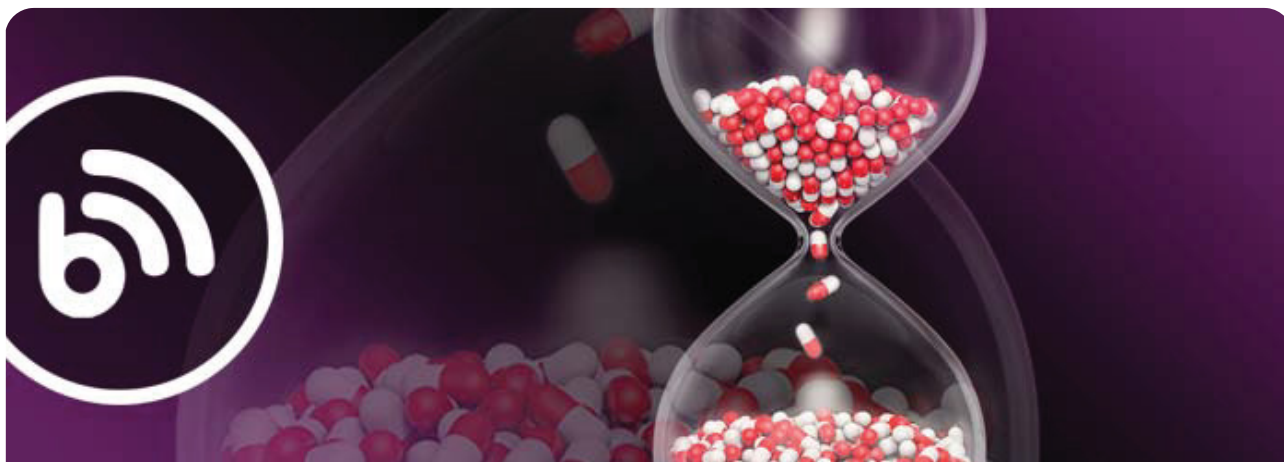PRIMARY MENU

The Certara Blog: PK/PD Modeling & Simulation

Why C_{max} is a Continuous Variable and T_{max} is a Categorical Variable

Posted on February 11, 2013 by Nathan Teuscher

The maximum observed concentration (C_{max}) and the time of C_{max} (t_{max}) are both obtained directly from the concentration-time data. In this post, I will review how to determine both of these parameters, and how to interpret information from the values. These two parameters are simple, but they pack some important information if you know how to extract it!
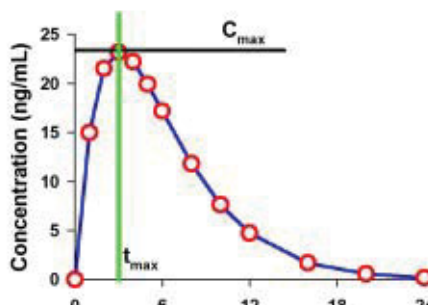
Andrx 2006

Time (h)

Example PK Curve with Cmax and tmax
labeled

C_{max}

This parameter is defined as the highest observed concentration in a concentration-time profile. In the image, the C_{max} is represented by the value of the black horizontal line, just below 25 ng/mL. If two peaks of identical height are observed, the first peak is considered the C_{max}. The C_{max} can be determined in most statistical software packages by using the MAX function which selects the maximum value of a set of data. The C_{max} is determined within the dosing interval. Thus if two doses are administered, you will have a C_{max} value following each dose administration (assuming blood draws were taken after both).

t_{max}

This parameter is defined as the time of the sample identified as C_{max}. In the image, the t_{max} is represented by the green vertical line. If two peaks of identical height are observed, the time of the first peak is considered t_{max}. Since each concentration is associated with a specific time in a pairwise fashion (time, concentration), the value for t_{max} is easily determined from the pair after the C_{max} is selected.

Both of these parameters are obtained from observational data. Neither is calculated from a mathematical model, and thus each reported value must exist in the original data set. For example, if you only drew blood samples at 0, 1, 2, 4, 6, and 8 hours, you could not have a t_{max} value of 3 hours. The actual time of blood sample collection is used rather than nominal (or planned) collection time.

The sampling scheme will have an enormous impact on the values determined for each of these parameters. As a general rule, the more frequently you sample around the expected time of the maximum concentration, the more accurate the value of C_{max} and t_{max} will be relative to the "true" values. In contrast, if only one sample is taken around the expected time of the maximum concentration, you will tend to see low variation in your t_{max} variable, and high variation in your C_{max} variable. This is because it is very unlikely that all subjects will have identical PK profiles, thus you are selecting a single time at which you make a measurement, and all variability is attributed to the C_{max} value.

This discussion now brings us to a critical point. The variable C_{max} is a continuous variable that can take any real number from 0 to infinity. Thus when using statistics to summarize C_{max} information, you can use normal probability theory. This means you can use averages and standard deviations to report summary statistics. I generally use geometric mean as the best representation of the population mean C_{max} value because these values are log-normally distributed (tailed distribution biased away from zer0). But arithmetic means are also acceptable to many. When comparing C_{max} values, you can use standard statistical tests based on normal distribution theory.

In contrast to C_{max}, the t_{max} variable is a categorical variable that can only take values based on the planned sampling scheme. Thus if your planned sample schedule includes 0, 1, 2, 4, 6, and 8 hours, you cannot have a sample at 1.5 or 10 hours (unless there was a deviation). Thus the expected values

for t_{max} are confined to some pre-selected categories. Thus when you summarize t_{max} results, you should NOT use averages and standard deviations, as they do not accurately describe the distribution of values. Instead, you should use medians and ranges. The median is the "middle" of the data, and the range represents the "extremes" of the data. This also applies to any statistical testing of t_{max} where you should use a non-parametric test like the Rank-Sum Test to compare t_{max} values from two different treatments (e.g. formulations).

So when designing your studies, make sure you take frequent samples around the time of the expected t_{max}, and always remember that C_{max} is a continuous variable, but t_{max} is a categorical variable.

To learn more about how to systematically leverage the many benefits of M&S across a drug development program, read this white paper.

White Paper:
Best Practices in Drug Development Modeling and Simulation

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ABOUT THE AUTHOR

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Dr. Nathan Teuscher is the Vice President of Pharmacometric Solutions at Certara. He is an expert in clinical pharmacology, pharmacometrics, pharmacokinetics and pharmacodynamics and was trained by David Smith at the University of Michigan. Dr. Teuscher has held leadership positions in biotechnology, pharmaceutical and contract research companies. In 2008 he established the Learn PKPD.com website to share his knowledge with the community. Prior to coming to Certara, he was the Founder and President of PK/PD Associates.

5 thoughts on "Why C_{max} is a Continuous Variable and T_{max} is a Categorical Variable"

1. **Vinodkumar** says:

August 22, 2017 at 2:31 am

Please clarify for me, on 2 median tmax in BABE studies, how to calculate medain tmax?

Reply

2. **Nathan Teuscher** says:

August 24, 2017 at 8:23 am

The median is calculated from a collection of values (see https://en.wikipedia.org/wiki/Median). Thus the median tmax is the median of all tmax values in the study. If you need to calculate twice the median, just multiply the median by 2.

Reply

3. **Jeffy Sarto** says:

February 6, 2018 at 12:27 am

What about T 1/2? Are descriptive statistics for T 1/2 other than median and range valid? Are they valid? If yes, then why? Thank you for the informative article, it was clear in explanation.

Reply

   1. **Nathan Teuscher** says:

   February 6, 2018 at 5:39 pm

   T1/2 is a transformation of the terminal rate constant, which is a continuous variable. Thus standard statistics (mean, standard deviation, etc.) are appropriate.

   Reply

4. **Angela** says:

February 28, 2018 at 4:12 am

Since the PK curve is described by several points, can we assume that the remaining concentrations (not only Cmax) are also log-normally distributed?

Reply

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