Predictor Identification in Time-to-Event Analyses

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Objective

Analysis of time-to-event data can provide valuable insight in designing appropriate dosing regimens to maximize the benefit/risk ratios. When these events occur relatively rapid in comparison to long term therapy, or time of onset is a primary outcome, identification of the appropriate predictors of exposure are paramount to accurately determining dosing. The aim of the analysis was to examine the influence of sample size, between subject variability on oral absorption and range of time-to-event parameter estimates on predictor identification.

Background

• The time required for a particular event that is not a continuous variable with normal distribution (onset of sleep; incident of vomiting) can be analyzed using a time-to -event analysis such as the Weibull distribution which is a generalization of the exponential distribution

• A typical model for the distribution of events is a Weibull model, characterized by 2 parameters, λ (scale) and α (shape):

$$Survival: \quad S(t) = e^{-(\lambda t)^{\alpha}}$$
$$Hazard: \quad h(t) = \lambda\alpha(\lambda t)^{\alpha-1}$$
$$Density: \quad f(t) = h(t) * S(t)$$

Methods

• Data was simulated from 175, 100 and 50 subjects receiving doses of 0, 0.3, 3, 6 and 10 mg in equal proportion.

• The pharmacokinetic model consisted of a 1-compartment model with CL= 0.01 (L/hr), V=10 (L) and Ka= 0.015 (hr^{-1}) with exponential BSV from 0-100% (Fig 1 with 40%BSV).

• Concentration was used as the predictor for the simulations based on an E_{max} model to describe drug effect:

$$h(t)_a = h(t) * \left(1 + \frac{E_{\max} * Conc}{EC_{50} + Conc}\right)$$

•Results in this poster correspond to E_{max}=5, λ=0.01 and α=1, with EC_{50} varying between 25 and 400. Similar trends were observed with different E_{max}, λ and α values.

•An alternative model with dose as the predictor was also considered and the power for model discrimination (based on AIC) as well as overall performance between the two predictors was compared.

$$h(t)_a = h(t) * \left(1 + \frac{E_{\max} * Dose}{ED_{50} + Dose}\right)$$

•Analysis was performed using NONMEM VI and PSN[1] computed the summary statistics between the two different predictors.

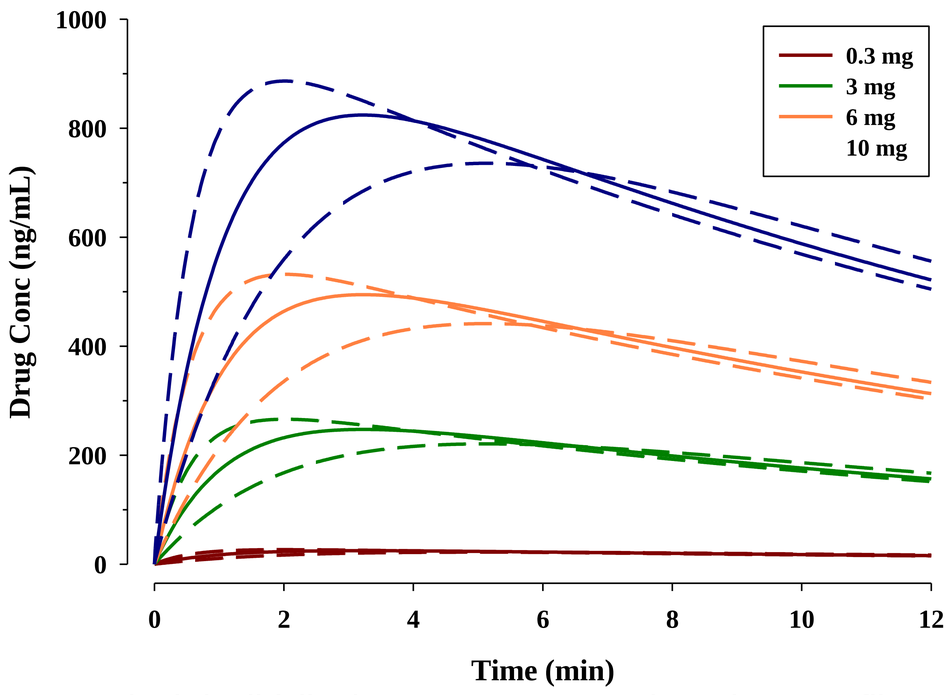

Figure 1. *Typical (solid line) Drug Concentration-Time Profile with 40% BSV on K_a (95% Percentile – dashed line)*

Results

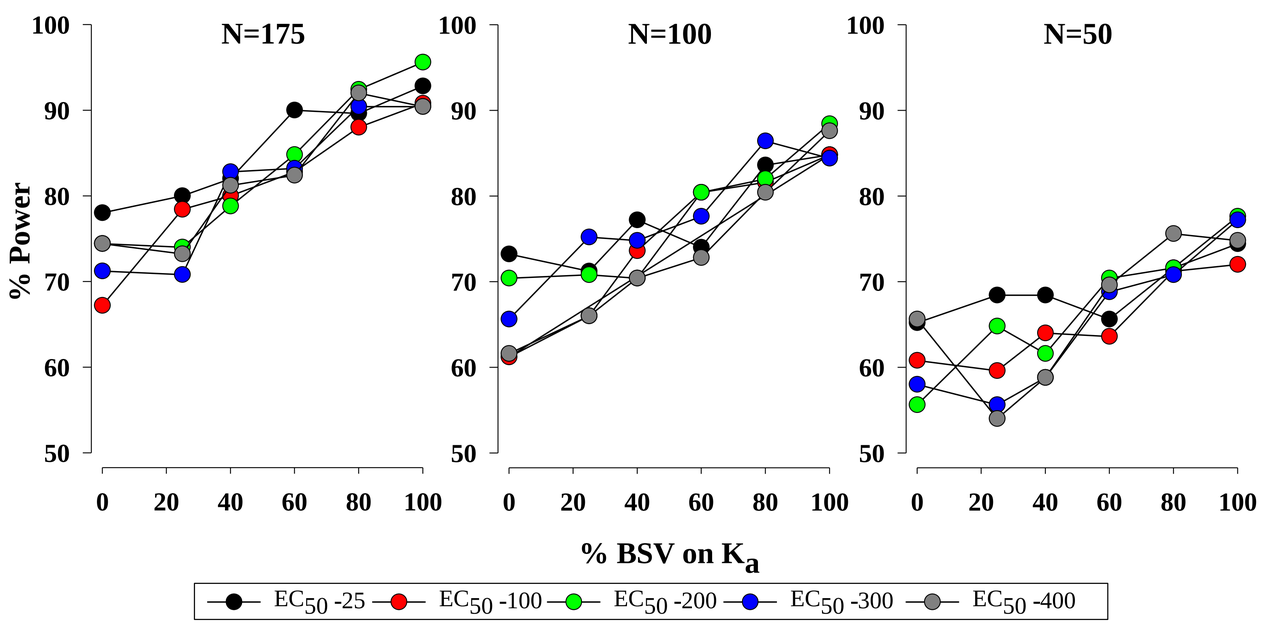

Figure 2. *% Power of Detecting Conc vs Dose as Predictor with Different BSV on K_a and Number of Subjects.*

• Power to correctly identify the true predictor (conc) improved with increasing levels of between subject variability and N (Fig. 2).

• Estimates for α and E_{max} were less biased from the true values when concentration was used as the predictor as compared to dose (Fig. 3).

• Estimated values of ED_{50} would predict a considerably higher dose needed to achieve similar response (Fig 4).

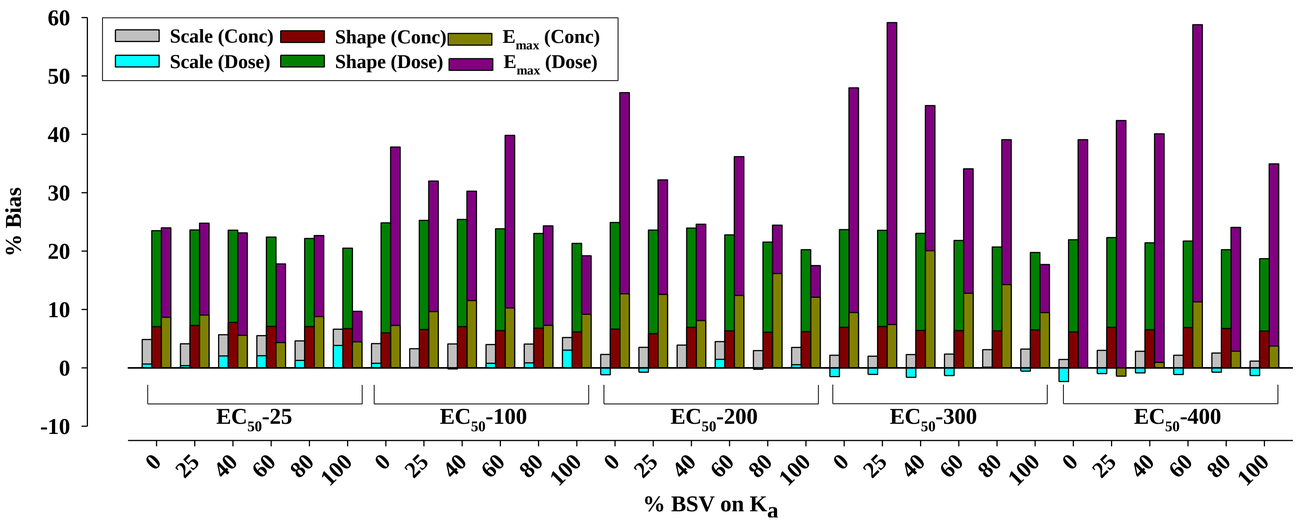

Figure 3. *% Bias (bars overlap & not stacked) of Parameter Estimates using Conc vs Dose as Predictor with Different BSV on K_a (N=175).*

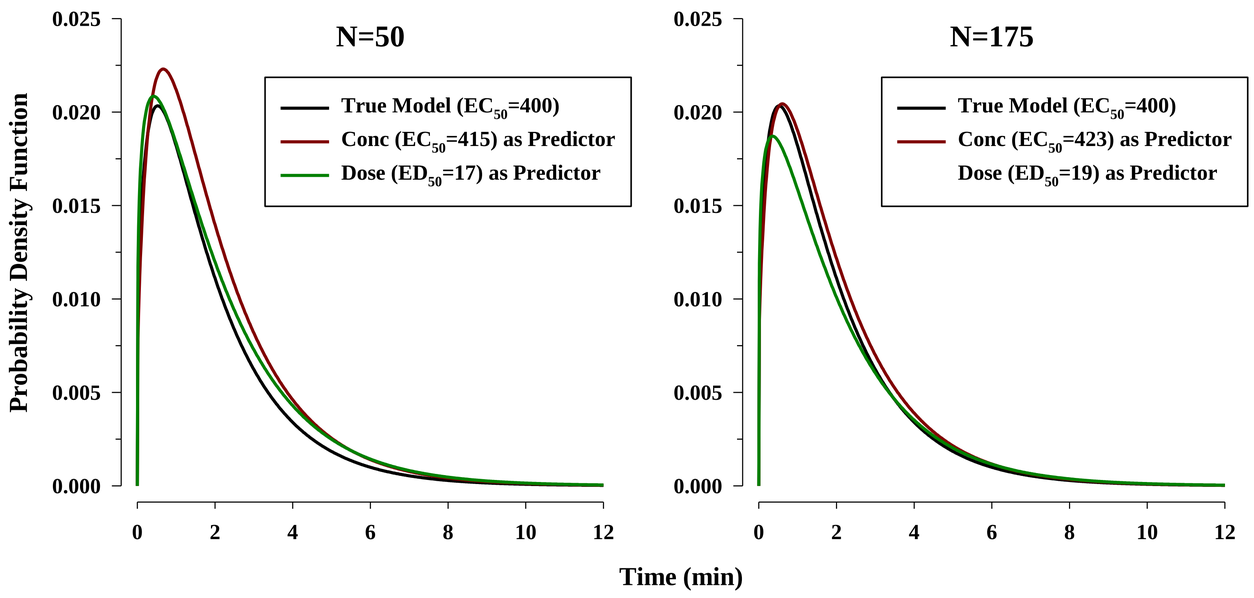

Figure 4. *Probability Density Function (PDF) vs.Time Profile after a 6-mg Dose.*

• Examination of the PDF demonstrated both predictors provided a reasonable concordance to the true model with respect to the median time of event.

Conclusion

Using dose as the predictor of time-to-event data (Weibull distribution) when the true effect is driven by concentration can provide a reasonable (or better) prediction of the PDF for TTE when sample sizes are relatively limited; however, doses based on the ED_{50} may be grossly over-estimated. As sample size increases the power for model discrimination increases as does the ability for concentration as predictor to more accurately describe the true PDF.

[1] Lindbom L, Ribbing J, Jonsson EN. Perl-speaks-NONMEM (PsN)--a Perl module for NONMEM related programming. Comput Methods Programs Biomed. 2004 Aug;75(2):85-94.