A comparison of methods for handling of data below the limit of quantification in NONMEM VI

Martin Bergstrand, Elodie Plan, Maria C. Kjellsson and Mats O. Karlsson
Division of Pharmacokinetics & Drug Therapy, Uppsala University, Sweden

Background

Common approaches for handling of concentration measurements reported as below the limit of quantification (BLQ), such as discharging the information or substitution with the limit of quantification (LOQ) divided by two, have been shown to introduce bias to parameter estimates [1-3].

In 2001, Stuart Beal published an overview of ways to fit a PK model in the presence of BLQ data [3]. New functionalities in NONMEM VI allow for simplified implementation of some methods presented in the publication. The method referred to as M2 applies conditional likelihood estimation to the observations above LOQ and the likelihood for the data being above LOQ are maximized with respect to the model parameters. This approach can be implemented in NONMEM VI by utilization of the YLO functionality [4].

By simultaneous modeling of continuous and categorical data where the BLQ data are treated as categorical, the likelihood for BLQ data to be indeed BLQ can be maximized with respect to the model parameters. The indicator variable F_FLAG can be used for to facilitate this approach in NONMEM VI. This method differs from the one Stuart Beal referred to as M3 in the sense that the likelihood is only estimated for BLQ data as opposed to all data.

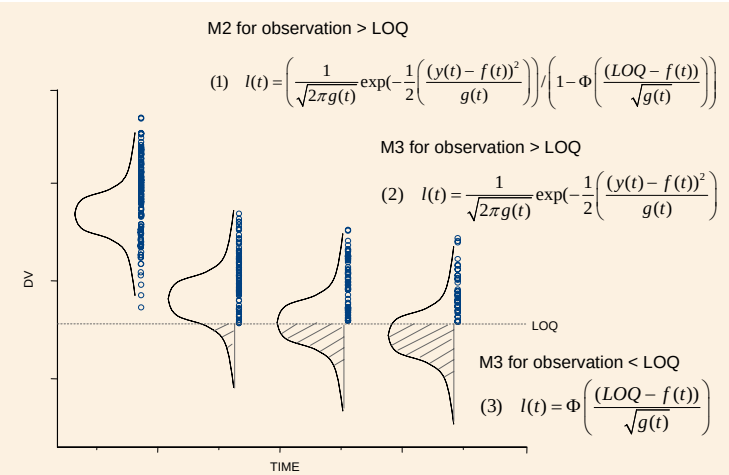

Figure 1. *Likelihood for observations (obs) above and below LOQ depending on observed dependent variable $y(t)$, model prediction $f(t)$, residual error variance $g(t)$ and LOQ. Method M3 maximizes the likelihood for BLQ obs being indeed BLQ (3) simultaneous to maximizing the likelihood for obs above LOQ (2). M2 maximizes the likelihood for obs above BLQ conditioned on that they are part of a truncated distribution (1).*

Methods

One hundred simulated population PK data sets, originally provided for a comparison of estimation methods in nonlinear mixed effects modeling (PAGE 2005)[5] were analyzed with 5 different methods for handling of BLQ data. The simulated datasets was based on a one-compartment model with first order absorption and first order elimination. A second group of 100 datasets was simulated according to a two-compartment intravenous bolus model. For both groups of datasets two different LOQ levels were assumed so that on average respectively 20% and 40% of the data were censored.

Five methods for handling of BLQ data were applied to the datasets; **A** BLQ data omitted **B** First BLQ observation substituted with LOQ/2 **C** YLO functionality (M2) **D** F_FLAG functionality **E** Maximum likelihood estimation for all data (M3) [3].

Results and Discussion

Methods **D** was overall most effective in reducing the BIAS introduced by censoring of BLQ data (Figure 2). This method also benefited from fewer problems with non-successful terminations than the other methods using Laplacian (Table I). However in the tested examples no systematic difference could be detected between estimates following successful/non-successful minimizations.

For the one-compartment example substitution with LOQ/2 (**B**) was shown to introduce BIAS. Whereas for the two compartment example, an expected improvement was seen for structural parameters and a positive bias on IIV for CL.

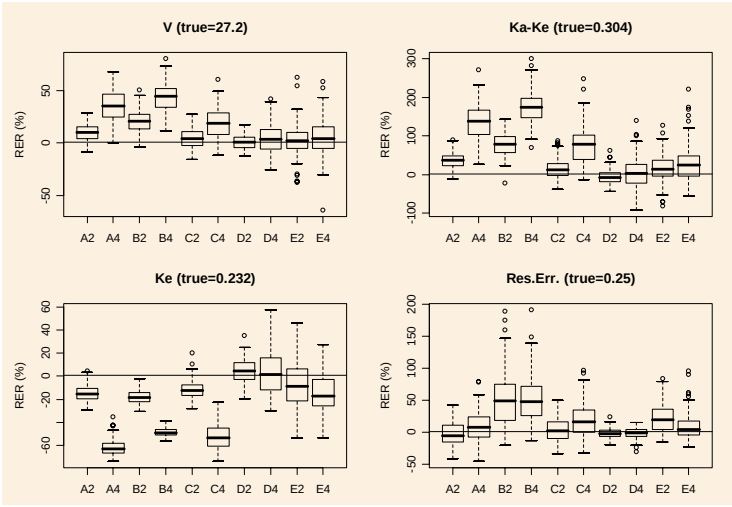

Figure 2. *One-compartment example, Relative Estimation Error (RER = (Est – True) / True × 100) for structural model parameters (V, Ke and Ka-Ke) and proportional residual error (Res.Err.). A2 => Method A, 20% <LOQ a.s.f.*

Table I. *Rate of successful minimizations and covariance steps with the applied methods for respectively model and percentage of BLQ observations*

Method	One-compartment mod				Two-compartment mod			
	Minimization		Covariance		Minimization		Covariance	
	20% BLQ	40% BLQ	20% BLQ	40% BLQ	20% BLQ	40% BLQ	20% BLQ	40% BLQ
A	100%	100%	38%	42%	95%	92%	85%	75%
B	97%	92%	25%	3%	97%	98%	68%	75%
C	87%	69%	9%	3%	69%	76%	19%	10%
D	94%	90%	15%	1%	92%	92%	30%	22%
E	34%	43%	17%	18%	64%	58%	34%	27%

Conclusions

- Likelihood-based methods for handling of BLQ data can offer improvement to parameter estimates.
- Best overall performance was seen using the F-FLAG functionality for method M3 (**D**).

References

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