Title: Approaches to Detect Non-Compliant Patients and Obtain Unbiased Estimates of Population PK Model Parameters in a Population with Prevalent Non-Compliance

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Objectives: To propose and evaluate methods for detection of non-compliance using concentration-time data and for obtaining unbiased estimates of population pharmacokinetic (PK) model parameters in a population with prevalent non-compliance.

Methods: Datasets that emulated three studies with different duration, sampling schemes and different levels of non-compliance were simulated. A two-compartment model with relatively fast first-order absorption (with 1-2 hours absorption half-life), relatively long terminal half-life (1 - 2 days), and significant drug accumulation during 4-weeks to 4-months treatment period of once-a-day dosing was used. Non-compliance was simulated as drug holidays (of several days) preceding some observations in 20 to 80% of subjects. For each dataset, the model without accounting for non-compliance was fitted first to evaluate bias of the parameter estimates. Then, two methods accounting for non-compliance were tested.

In the first method (referred to as the ETA-on-epsilon method), a random effect on the magnitude of the residual error was introduced. High magnitude of the residual error estimated for some subjects was thought to be associated with non-compliance in these subjects. The same model was fitted to the simulated datasets where increasing fractions of subjects with the highest residual errors were commented out. Association of non-compliant subjects with high-residual-error subjects was investigated. Parameter estimates of these models were compared with the true (used for simulations) parameters and the parameters of the model that did not account for non-compliance.

The other method (referred to as the “profiles” method) was developed for the data with a specific sampling pattern that included an outpatient (non-compliant) part with several trough samples followed by the rich profile after the inpatient (compliant) dose. The method is the generalization of the idea proposed in [1] that relies only on the doses known to be administered (e.g., inpatient doses). In this method, all concentration measurements during the outpatient part of the study (except the trough value immediately preceding the inpatient dose) are removed from the dataset and an additional parameter (relative bioavailability of the outpatient doses) is introduced. This allows decoupling of the unreliable (outpatient) and reliable (inpatient) dosing and concentration data. In case of a one-compartment drug, the method reduces to that proposed in [1]. The parameter estimates obtained using this method were compared with the true parameters. Association of the individual estimate of relative bioavailability during the outpatient part of the study with the compliance status during this period was investigated. The ETA-on-epsilon method was also tested on the data used for the profiles method.

Results: Investigation of the ETA-on-epsilon method indicated that the parameter estimates of the model that did not account for non-compliance could be significantly biased, especially for the datasets that included high fraction of non-compliant patients. Introduction of the ETA-on-epsilon parameter significantly reduced the bias. Individual ETA-on-epsilon values allowed identification of non-compliant subjects. When subjects with high magnitude of the residual error were removed from the dataset, bias due to non-compliance was further reduced. During incremental removal of the subjects with the highest ETA-on-epsilon values the population parameter estimates converged to the true values until bias disappeared. At the same time, variance of the ETA-on-epsilon random effect became smaller and then disappeared indicating that the ETA-on-epsilon random effect indeed was caused by non-compliance. However, precision of the obtained parameter estimates decreased for the datasets with high fraction of non-complaint subjects that needed to be removed from the dataset to obtain unbiased parameter estimates.

Investigation of the profiles method indicated that it allowed for the unbiased estimates of the model parameters in the datasets with any fraction of non-compliant patients. However, the method heavily relied on the availability of rich data following the inpatient dose. Simulated non-compliant subjects were estimated to have low bioavailability during the outpatient part of the study. Thus, the estimates of bioavailability can be used as an indication of compliance during time preceding the inpatient dose.

The proposed methods allowed identification of subjects with non-compliance and reduced or completely eliminated bias in the parameter estimates for the simulated datasets with various sampling schemes and fractions of non-complaint patients. Applications of these methods to real data are ongoing.

The two proposed methods can be viewed as complimentarily tools, each with its own advantages and limitations. The profiles method should provide unbiased parameter estimates for any non-compliance pattern but it can be applied only for the specific sampling schemes that include relatively rich data following the inpatient (fully compliant) dose. The ETA-on-epsilon method is not based on any assumptions about the sampling schemes but it is unlikely to account for the completely random non-compliance if it is present in the majority of patients.

Conclusions: For a number of simulated datasets with various sampling schemes and various fractions of non-compliant patients, the proposed ETA-on-epsilon and profiles methods allowed to identify subjects with compliance problem and to obtain the unbiased estimates of model parameters. Even without additional modifications, inclusion of the inter-individual random effect on the residual error resulted in a significant reduction of the estimation bias. The proposed methods offer a way to evaluate the influence of compliance on the population PK parameter estimates.

References:

[1] Gupta P, Hutmacher MM, Frame B, Miller R, An alternative method for population pharmacokinetic data analysis under noncompliance. J Pharmacokinet Pharmacodyn. 2008;35(2):219-33.