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Application of Identifiability Analysis Algorithm to Population PK of the Drug with Target-Mediated Drug Disposition

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Poster: Methodology- Algorithms

Background: The pharmacokinetic model for drugs exhibiting target-mediated disposition (TMDD) was suggested in [1]. Several simpler approximations of the TMDD model were proposed in [2,3]. The Quasi-Equilibrium (QE) [2] and the Quasi-Steady-State (QSS) [3] approximations apply when the drug-target-complex system rapidly reaches equilibrium and steady-state, respectively. The Michaelis-Menten (MM) [3] approximation applies when concentrations of the free drug significantly exceed concentrations of the target and/or target occupancy is very high [3]. In cases when one of the approximations provides a good description of the data, the more complicated models are over-parameterized especially when only the free or total (but not both) drug concentration measurements are available. An algorithm to test identifiability of the TMDD model parameters for a particular data set and to choose a correct (non-over-parameterized) approximation was suggested in [3].

Objectives: To test the proposed Identifiability Analysis Algorithm on an example dataset simulated from a TMDD model based on clinical data.

Methods: The simulated dataset included 150 densely sampled patients who received IV or SC doses ranging from 200 to 7000 units. Study design, sampling scheme, and the parameters of the TMDD model used for simulations were chosen to reflect the actual clinical data (with re-scaled parameters). Only free drug concentration was measured. First, the Identifiability Analysis Algorithm was implemented as following. The TMDD model was fitted to the data, and the obtained parameter estimates were used to simulate the concentration-time profiles for the TMDD and corresponding QE, QSS and MM models. The results of the simulations were used to identify: i) the simplest model equivalent to the TMDD model; ii) the identifiable combination of the TMDD model parameters; iii) the dosing regimens and the concentration levels that can be described by the MM model. Then, the QE/QSS and MM models were directly fitted to the data. The individual and population predictions of these models were compared with the predictions of the TMDD model. Precision of the parameter estimates was investigated using the bootstrap procedure. Conclusions of the Identifiability Analysis were compared with the results of the direct investigation of the TMDD, QE/QSS and MM models.

Results: Based on the TMDD model parameter estimates, QE, QSS and MM approximations were shown to be identical to the full TMDD model for all dosing regimens of interest. When fitted independently to the same data, all models provided nearly identical population and individual predictions. The TMDD and QE/QSS model parameters were strongly correlated. Significant correlation was observed even for the MM model parameters (V_{MAX} and K_M).

Conclusions: For the investigated dataset, the TMDD model parameters cannot be determined based on the available data. The MM approximation provides an adequate description of the data. No improvement can be obtained using more complicated QE and QSS approximations, or the TMDD model. Identifiability Analysis Algorithm allows selection of the parsimonious model that describes the available data.

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