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Approximations of the Target-Mediated Drug Disposition Model and Identifiability of Model Parameters

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Poster: Methodology- Algorithms

Objectives: To suggest simpler forms of the model [1] that describes pharmacokinetics of the drugs with target-mediated disposition (TMDD); to derive relationships between parameters of the full and simpler models; to investigate range of applicability of these simpler models; to propose an algorithm for determining the identifiability of the models for drugs with TMDD.

Methods: Two approximations of the TMDD model were derived. The Quasi-Steady-State (QSS) model was obtained similarly to the Quasi-Equilibrium (QE) model [2] with the assumption of quasi-equilibrium of the free drug, target and complex replaced by the assumption of quasi-stationarity of these entities. The QSS and QE equations are identical but dissociation constant $K_D=K_{OFF}/K_{ON}$ is replaced (for the QSS model) by the quasi-stationarity constant $K_{SS}=(K_{OFF}+K_{INT})/K_{ON}$. Further simplification was obtained assuming that the free drug concentration significantly exceeds the concentration of the target and that internalization (or complex degradation) constant K_{INT} is sufficiently large. Then, the TMDD model degenerates to the model with Michaelis-Menten (MM) elimination. MM parameters can be expressed as $V_{MAX}=R_{Total}\ K_{INT}$ and $K_m=(K_{OFF}+K_{INT})/K_{ON}$ where R_{Total} is the total concentration of the target.

Results: The following algorithm is proposed for modeling of drugs with TMDD and investigation of identifiability of model parameters: (1) Fit the TMDD model and estimate the model parameters; (2) For dosing conditions typical for the analysis dataset simulate concentration-time profiles for all models (TMDD and corresponding QE, QSS and MM) using parameters obtained in Step 1. Then the following rules would result: (1) The simplest model that is equivalent to the TMDD model should be used; (2) If any simpler models provide predictions identical or similar to the predictions of the TMDD model, then the parameters of the TMDD model are not uniquely defined, and the obtained parameter estimates are not reliable. Only parameter combinations specified by the simplest of the equivalent models can be considered reliable. (3) If precise estimates of the TMDD model parameters are needed, more data should be collected in the range of concentrations and for dosing regimens where the simpler approximations (QE, QSS or MM) deviate from the TMDD model; (4) Even if the TMDD model deviates from the simpler model for some concentration ranges and some dosing regimens, the simpler model can be used if this model predictions are equivalent to the predictions of the TMDD model for the therapeutic range of doses and/or concentrations. If the TMDD model cannot provide any parameter estimates, the algorithm may start from the fit of the QE/QSS model. QE/QSS parameter estimates can then be used to derive the simpler MM model and to develop the full TMDD model using partial knowledge of the TMDD parameters obtained from the QE/QSS fit.

Simulation examples indicate that the QSS model is preferable to the QE model when internalization rate significantly exceeds dissociation rate. The MM approximation is sufficient when the drug concentration significantly exceeds receptor concentrations or when the target occupancy is very high.

Conclusion: The QSS model is a good approximation of the TMDD model when internalization rate of the complex significantly exceeds dissociation rate. The MM approximation provides adequate PK description when free drug concentrations significantly exceed concentrations of the target or when the target occupancy is very high. The proposed algorithm for determining the identifiability of the TMDD model may provide justification for use of the simpler approximations, avoiding use of incorrect parameter estimates of over-parameterized TMDD models while simultaneously saving time and resources required for the population analysis of drugs with the target-mediated disposition.

References:

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