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Pharmacodynamic Modeling of Biologics with Target-Mediated Drug Disposition: TMDD Approximations, Relation to Indirect-Response Models, and Application to Population PK-PD Analyses

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Poster: Methodology- Other topics

Objectives: To investigate the rapid binding (RB), quasi-steady-state (QSS) and Michaelis-Menten (MM) approximations [2,3] of the TMDD model [1] as applied to the pharmacodynamic (PD) data; to derive relationships between the parameters of the TMDD and indirect response models; to investigate and compare applicability of the TMDD approximations in cases when the drug-target complex is eliminated faster or slower than the free target; to test the identifiability analysis algorithm [3] on the example of the simulated population PK-PD data.

Methods: a) TMDD equations and its approximations were reviewed and compared with the indirect-response model equations. b) For several combinations of model parameters, concentrations of the drug, target, and drug-target complex were simulated from the TMDD model and the corresponding RB, QSS, and MM approximations. Simulated concentration-time profiles were compared to investigate the ability of the approximations to describe the TMMD model predictions. c) The population PK-PD dataset that included the data from two studies was simulated. The first study imitated the fist-in-man, dose-escalation, rich sampling study with 4 cohorts of six subjects administered single dose of 100, 300, 1000, or 3000 nmol. The second study imitated a phase 2 study with 2 arms of 100 subjects administered three doses of 1000 or 3000 nmol with 4 week intervals. Free drug concentrations and total target concentrations were measured. Identifiability of the TMDD model parameters and ability of the approximations to describe the simulated data, to estimate the TMDD model parameters, and to predict unobservable free target concentrations were investigated.

Results: a) When the free target is eliminated faster (or slower) than the drug-target complex, the equation for the total target concentration was shown to coincide (for RB, QSS, or MM approximations) with the indirect response models with stimulation (or, respectively, inhibition) of elimination. Correspondence between the TMDD and indirect-response models allows estimating unobservable free target concentrations using the indirect-response model parameters. b) For the investigated range of parameters, the RB and QSS approximations behaved similarly: they provided an adequate description of the data simulated from the TMDD model. The MM approximation was applicable when the degradation rate of the drug-target complex exceeded the degradation rate of the free target, and was not appropriate otherwise. c) In the population PK-PD simulation, the TMDD model, as expected, was able to estimate all model parameters except the binding constants. For the binding constants, the ratio was estimated with a good precision while the values themselves remained close to the initial estimates and far from the true values. The RB and QSS approximations were able to recover the true model parameters and estimate the drug, target, and complex concentrations correctly. As the MM approximation was not applicable (the drug-target complex concentration was comparable to the free drug concentration), the combination of the PK model with MM elimination (to describe free drug concentrations) and the indirect response model with inhibition of elimination (to describe total target concentrations) was tested. The PK model provided unbiased individual predictions of the free drug concentration. However, random effects on the MM parameters strongly depended on dose, and population predictions for low-dose groups were biased. The indirect-response PK-PD model (using individual predictions of drug concentrations) precisely estimated the relevant TMDD model parameters, providing unbiased population and individual predictions of the total and free target concentrations.

Conclusions: In the variety of tested examples, the rapid binding and quasi-steady-state approximations provided excellent description of the PK and PD data simulated from the TMDD model. Equation for the total target concentration derived based on these approximations coincides with the indirect-response model with inhibition or stimulation of elimination. The simulated population PK-PD study demonstrated that for drugs with TMDD, parameters of the indirect response models can be used to estimate unobservable free target concentrations that are important for pharmacodynamic modeling.

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Return to the Publications Page

Return to the Main Page