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TMDD Model for Drugs that Bind Soluble and Membrane-Bound Targets: Can Quasi-Steady-State Approximation Estimate Unobservable Membrane-Bound Target Occupancy?	
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Poster: Methodology- Other topics	
<p><b>Objectives:</b> To develop an approach for description of drugs with target-mediated drug disposition (TMDD) that bind to soluble (S) and membrane-bound (M) targets; to demonstrate on the simulated example that models based on the quasi-steady-state (QSS) approximation can identify parameters of both targets based on the free drug and the total S-target concentrations.</p> <p><b>Methods:</b> The TMDD equations [1] were extended to describe drug interactions with multiple targets. The QSS approximation [2-4] of these equations was derived. A population data set (3250 unbound drug and 3305 total S-target concentrations from 224 subjects) was used to investigate identifiability of QSS model parameters. The drug and target concentrations were simulated for a monoclonal antibody that can bind to S and M targets. It was assumed that either unbound or total (unbound and bound to the S-target) drug concentration and the total S-target concentrations are observable while the M-target is not observable. The QSS approximation of the two-target TMDD model was used to fit the simulated data. Dependence of results on the relative contribution of the targets to drug elimination and on assay properties (limit of quantification) was also investigated.</p> <p><b>Results:</b> For the range of parameters typical for monoclonal antibodies with binding to S and M targets, S-target binding was described by the QSS approximation while Michaelis-Menten elimination term adequately described contribution of the M-target. Contributions of the two targets could not be separated when only the drug concentration data were available. However, when the S-target concentration data were also available, the model correctly estimated parameters of the drug and both targets, including the M-target production rate and the percent decrease from the baseline level of unbound M-target concentration. The parameters were estimated precisely, with the highest bias (10-15%) and the lowest precision (RSE=10-18%) observed for the M-target parameters. Results were the same whether the total or unbound drug concentrations were available, and whether the assay quantification limits were 0.1 nM or zero. When synthesis rate of the M-target was much smaller than that of the S-target, M-target parameters could not be identified in the absence of the M-target measurements.</p> <p><b>Conclusions:</b> The TMDD model and its approximations were derived for drugs that bind to more than one target. Single-subject simulations for a monoclonal antibody that binds to soluble and membrane-bound targets demonstrated that QSS approximation provided an excellent description of the data simulated from the full two-target TMDD model. Population-level simulations demonstrated identifiability of the two-target QSS model parameters, specifically, the ability of the model to obtain precise and unbiased parameter estimates for the drug, and both soluble and membrane-bound targets. Moreover, the model correctly estimated unobservable M-target production rate and percent decrease from baseline of the unbound M-target concentration. However, identification of the M-target parameters was reliable only when the synthesis rate of this target was comparable or higher than the synthesis rate of the S-target.</p> <p><b>References:</b>  [1] Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. <i>J. Pharmacokinetic and Pharmacodynamic</i> (2001), Vol. 28, pp. 507-532.  [2] Gibiansky L, Gibiansky E, Kakkar T, Ma P: Approximations of the target-mediated drug disposition model and identifiability of model parameters. <i>J. Journal of Pharmacokinetics Pharmacodynamics</i> (2008), 35(5):573-91.  [3] Gibiansky L, Gibiansky E, Target-Mediated Drug Disposition Model: Approximations, Identifiability of Model Parameters, and Applications to the Population Pharmacokinetic – Pharmacodynamic Modeling of Biologics, <i>Expert Opinion On Drug Metabolism and Toxicology</i> (2009), 5(7): 803-812.  [4] Gibiansky L, Gibiansky E, Target-Mediated Drug Disposition Model: Relationships with Indirect Response Models and Application to Population PK-PD Analysis, <i>Journal of Pharmacokinetics and Pharmacodynamics</i> (2009), 36(4): 341-351.</p>	

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