Title: Modeling of Drugs with Soluble (S) and Membrane-Bound (M) Targets using Quasi-Steady-State (QSS) Approximation of the Target-Mediated Drug Disposition (TMDD) Model.

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Purpose: To develop an approach for description of drugs with TMDD that simultaneously bind to S and M targets; to demonstrate on the simulated example that models based on the QSS approximation can identify parameters of both targets based on the free drug and the total S-target concentrations.

Methods: The TMDD equations were extended to describe drug interactions with multiple targets. QSS approximation 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. Drug and target concentrations were simulated for a monoclonal antibody that can bind to S and M targets. It was assumed that the unbound drug concentration and the total S-target concentrations are observable while the M-target is not observable. The QSS approximation of the TMDD two-target model was used to fit the simulated data.

Results: 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 (MM) elimination term adequately described contribution of the M-target. Contributions of two targets could not be separated when only the drug concentration data were available. However, when 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.

Conclusions: The TMDD model and its approximations were derived for drugs that bind to two different targets. Simulation study for a monoclonal antibody that binds to soluble and membrane-bound targets 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.