Target-Mediated Drug Disposition Model for Drugs with Multiple Targets

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OBJECTIVES

- To present the target-mediated drug disposition (TMDD) model for drugs that bind to more than one target;
- To derive the rapid binding (RB), quasi-steady-state (QSS) and Michaelis-Menten (MM) approximations of TMDD equations;
- To investigate drug and target concentration-time profiles for these systems;
- To investigate identifiability of parameters for a two-targets TMDD model using simulations.

METHODS

- Equations that describe drugs with TMDD [1] were extended to describe drug interactions with more than one target;
- Approximations (RB, QSS and MM) [2-4] of these equations were derived;
- Concentration-time profiles of the free drug, free and total target concentrations were simulated for a monoclonal antibody that can bind to two different targets;
- Data (drug concentration and total concentration for one of the targets) simulated using TMDD equations with two targets were fit to the QSS model with 1 or 2 targets to investigate identifiability of model parameters.

RESULTS

QSS Equations

For a two-compartment model where drug (administered as IV bolus dose D_2 and SC dose D_1) binds to i=1, N targets with different affinities and different turnover characteristics:

$$\frac{dA_d}{dt} = -k_a A_d; \qquad A_d(0) = F_1 D_1; \qquad C_{tot}(0) = \frac{D_2}{V};$$

$$\frac{dC_{tot}}{dt} = \frac{In(t) + k_a A_d + k_{tp} A_T}{V} - (k_{el} + k_{pt})C - \sum_{i=1}^{N} \frac{R^i{}_{tot} k^i{}_{\text{int}} C}{K^i{}_{SS} + C};$$

$$\frac{dA_T}{dt} = k_{pt} CV - k_{tp} A_T; \qquad A_T(0) = 0;$$

$$\frac{dR^i{}_{tot}}{dt} = k^i{}_{syn} - k^i{}_{\deg} R^i{}_{tot} - (k^i{}_{\text{int}} - k^i{}_{\deg}) \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}; \quad R^i{}_{tot}(0) = \frac{k^i{}_{syn}}{k^i{}_{\deg}}.$$

C, R^i, and R^iC are concentrations of the free drug, free i^{th} target, and drug - i^{th} target complex in the central compartment; k_{el} is linear elimination rate constant; k^i_{on}, k^i_{off}, and k^i_{int} are i^{th} target binding, dissociation, and internalization rate constants; k^i_{deg} and k^i_{syn} are i^{th} target degeneration and production rate constants; $K_{iSS}=(k^i_{off}+k^i_{int})/k^i_{on}$ are the steady-state constants; V is central compartment volume; $C_{tot}=C+\text{sum}_i R^iC$ and $R^i_{tot}=R^i+R^iC$ are total concentrations of the drug and the i^{th} target in the central compartment. These quantities are related by the equations:

$$R^iC = \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}; \quad R^i = \frac{R^i{}_{tot} K^i{}_{SS}}{K^i{}_{SS} + C}; \quad C_{tot} = C + \sum_{i=1}^{N} \frac{R^i{}_{tot} C}{K^i{}_{SS} + C}.$$

Unusual drug and target concentration profiles

Interaction of the drug with two targets may lead to a rebound of the free target concentration for one of the targets above the pre-dose values (Figure 1), a phenomenon usually attributed to a feedback mechanism.

Identifiability of Model Parameters (Single-Subject Simulations)

- The data for a drug that binds to two targets were simulated from the full TMDD model. Target 1 was at quasi-steady state, while target 2 contribution was equivalent to the Michaelis-Menten approximation. Single-subject simulations with 4 different doses were performed.
- When only PK data were available, the system with two targets was not distinguishable from the system with one target (Figure 2). The estimated target parameters of the one-target TMDD system were different from the parameters of the original targets.
- When the total concentrations of target 1 and the PK data were available:
  - ✓ The QSS model was able to estimate all parameters correctly;
  - ✓ Attempts to fit a one-target QSS model to the target 1 and PK data generated by the two-target TMDD model were not successful;
  - ✓ However, a one-target PK model was able to describe the PK data. An indirect-response model that used these PK predictions correctly estimated the parameters of the target.

Figure 1. Predictions from the TMDD (solid lines) and QSS (dashed lines; coincide with the solid lines) models for a drug that binds to two targets

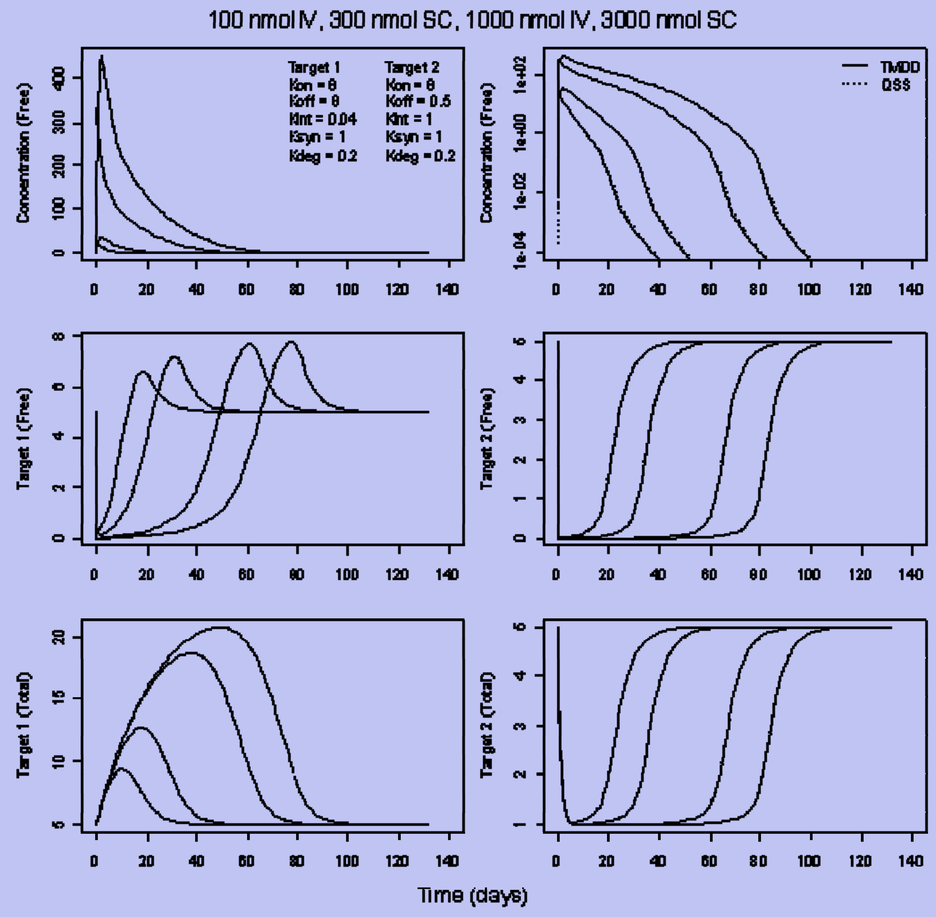
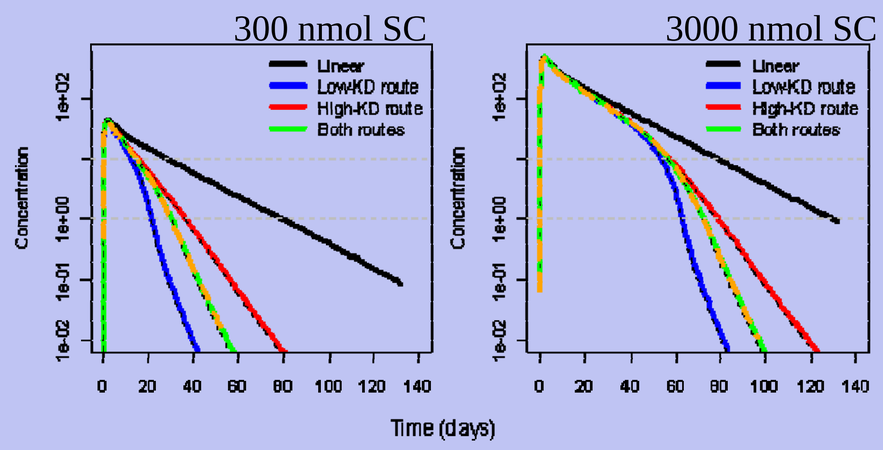


Figure 2. Predictions of free drug concentrations from the TMDD model with two targets and the Michaelis-Menten model with one target when only the PK data is available



Black line: TMDD model predictions when target-mediated elimination is absent; **Red line**: TMDD model predictions for one-target system with high K_D; **Blue line**: TMDD model predictions for one-target system with low K_D; **Green line**: TMDD model predictions for two targets; **Orange dash line**: Michaelis-Menten model predictions for one-target system; Black thin dash lines: QSS approximations of the corresponding models.

CONCLUSIONS

- TMDD equations and its approximations were derived for the drug that binds to two or more different targets;
- Simulated examples demonstrated validity of the quasi-steady-state approximation of this system;
- Simulations for a monoclonal antibody that binds two targets revealed unusual kinetic properties of the drug and the targets, including possible rebound of one of the targets above the baseline level;
- Target parameters of the TMDD models with more than one target were not identifiable based on the PK data alone. Concentrations data of at least one target were required to identify parameters of the two-targets TMDD model.

REFERENCES

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[4] Gibiansky L, Gibiansky E: TMDD Model: Approximations, Identifiability of Model Parameters, and Applications to the Population PK-PD Modeling of Biologics. Expert Opinion Drug Metab Tox., 5(7) 2009.