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

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Objectives

- To suggest simpler forms of the model [1] that describes pharmacokinetics of the drugs with target-mediated drug disposition (TMDD);
- To derive relationships between the parameters of the full and simpler models;
- To investigate the 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:

- Fit the TMD model and estimate the model parameters;
- 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:

- The simplest model that is equivalent to the TMDD model should be used;
- If any simpler models provide predictions identical or similar to the predictions of the TMD 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.
- 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;
- 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 its 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 indicates 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.

Conclusions

- 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

1. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J. Pharmacokinetic and Pharmacodynamic 28: 507-532 (2001).

2. Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. Pharmaceutical Research, 22 (10): 1589-1596 (2005).

Enzyme Kinetics Equations

TMD Model : $$\frac{dC_{Complex}}{dt} = K_{ON}C_{FreeDrug}C_{Target} - (K_{Int} + K_{OFF})C_{Complex}$$

QE Approximation: $$K_{ON}C_{FreeDrug}C_{Target} - K_{OFF}C_{Complex} = 0$$

QSS Approximation: $$K_{ON}C_{FreeDrug}C_{Target} - (K_{Int} + K_{OFF})C_{Complex} = 0$$

Quasi-Equilibrium or Quasi-Steady-State:

$$\frac{dC_{Total}}{dt} = input - K_{Int}C_{Total} - (K_{Drug} - K_{Int})C_{FreeDrug};$$

$$\frac{dR_{Total}}{dt} = R_{Syn} - K_{Deg}R_{Total} - (K_{Int} - K_{Deg})(C_{Total} - C_{FreeDrug}).$$

Quasi-Equilibrium:

$$\frac{C_{FreeDrug}C_{Target}}{C_{Complex}} = \frac{K_{OFF}}{K_{ON}} = K_D;$$

$$C_{FreeDrug} = \frac{1}{2}\left[(C_{Total} - R_{Total} - K_D) + \sqrt{(C_{Total} - R_{Total} - K_D)^2 + 4K_DC_{Total}}\right]$$

$$C_{Complex} = \frac{R_{Total}C_{FreeDrug}}{K_D + C_{FreeDrug}}.$$

Quasi-Steady-State:

$$\frac{C_{FreeDrug}C_{Target}}{C_{Complex}} = \frac{K_{Int} + K_{OFF}}{K_{ON}} = K_{SS};$$

$$C_{FreeDrug} = \frac{1}{2}\left[(C_{Total} - R_{Total} - K_{SS}) + \sqrt{(C_{Total} - R_{Total} - K_{SS})^2 + 4K_{SS}C_{Total}}\right];$$

$$C_{Complex} = \frac{R_{Total}C_{FreeDrug}}{K_{SS} + C_{FreeDrug}}.$$

Michaelis-Menten Approximation:

$$\frac{dC_{FreeDrug}}{dt} = input - K_{Drug}C_{FreeDrug} - \frac{R_{Total}K_{Int}C_{FreeDrug}}{K_{SS} + C_{FreeDrug}};$$

$$\frac{dR_{Total}}{dt} = R_{Syn} - K_{Deg}R_{Total} - (K_{Int} - K_{Deg})\frac{R_{Total}C_{FreeDrug}}{K_{SS} + C_{FreeDrug}}.$$

Parameters used for simulations (Figures 1-4) . It was assumed that the total target concentration R_{Total} is constant, and V=1.

Case	K_{ON}	K_{OFF}	K_{INT}	R_{Total}	$K_D=K_{OFF}/K_{ON}$	$K_{SS}=K_M=(K_{OFF}+K_{INT})/K_{ON}$	$V_{MAX}=R_{Total}K_{INT}$
1	0.1	0	2	10	0	20	20
2	0.1	2	2	10	20	40	20
3	0.5	0.5	2	10	1	5	20
4	0.1	0	0.2	100	0	2	20
5	0.1	2	0.2	100	20	22	20
6	0.5	0.5	0.2	100	1	1.4	20
7	0.1	0	0.02	1000	0	0.2	20
8	0.1	2	0.02	1000	20	20.2	20
9	0.0001	0.1	3	1000	1000	31000	3000

Discussion of simulation results

- The QSS model provides better description of the TMDD data (relative to the QE model) when $K_{INT} > K_{OFF}$ (Figure 1-4);
- The MM model provide adequate description of the TMDD data when $\mathbf{R_{Total}}$ is small when compared to the characteristic concentration range (Figure 1 and Figure 3, high concentrations);
- The MM predictions may diverge from the true concentrations when the drug concentrations fall below $\mathbf{R_{Total}}$(Figure 2 and Figure 4).

Implications for modeling of drugs with the TMDD

- Investigation of identifiability of the TMDD model parameters for each specific data set: only parameters of the parsimonious model are reliable while all the other parameter estimates should not be trusted;
- Simulations can identify dosing regimens and concentration ranges that need to be explored to identify all TMDD parameters: regimens where predictions of the simpler models diverge from the TMDD model predictions are of interest;
- Results allow selecting the parsimonious model that is sufficient to describe the data for the therapeutic dosing regimens. Even if the TMDD model is necessary to describe the entire range of tested doses, only simpler model might be necessary to describe the pharmacokinetic of the drug in the therapeutic range of concentrations and for the clinically relevant dosing regimens;
- The proposed method was tested on the example of the simulated dataset as described in Poster # 1271.

Figure 1 (Case 1-3):
Low Target Concentration, Low dose

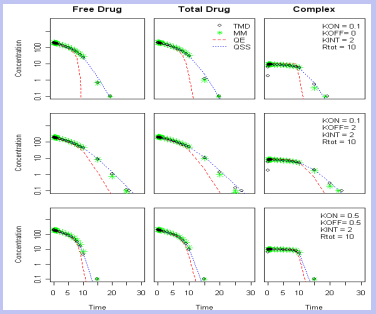


Figure 2 (Case 4-6):
Medium Target Concentration, Low Dose

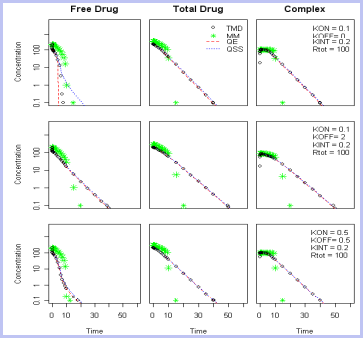


Figure 3 (Case 4-6):
Medium Target Concentration, High Dose

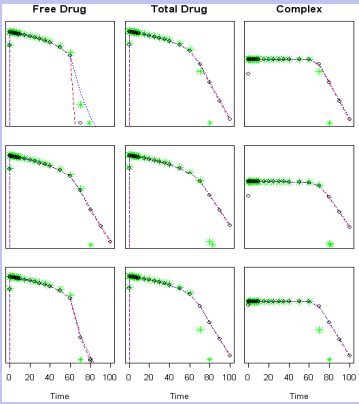
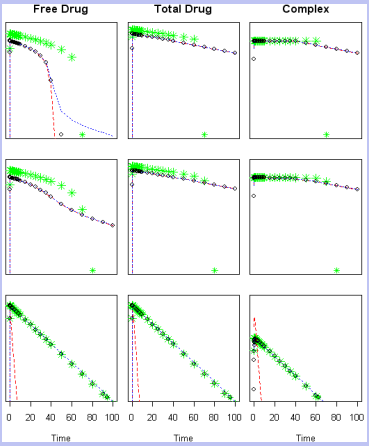


Figure 4 (Case 7-9):
High Target Concentration, High Dose



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