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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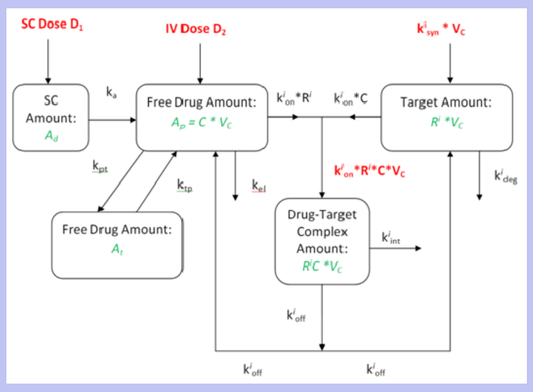
OBJECTIVES

- 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.

METHODS

Multi-Target TMDD: Red: input; ***Green****:* amounts; **Black**: rate constants.
Target *i* is shown. **Flux** = **rate** * **amount**



Two-target (S and M) QSS equations

$$\frac{dA_d}{dt} = -k_a A_d; \quad A_d(0) = D_1; \quad C_{tot} = C + R^S C; \quad R_{tot} = R + R^S C;$$

$$\frac{dC_{tot}}{dt} = \frac{F_{SC} k_a A_d + k_{tp} A_T}{V_c} - \left(k_{el} + k_{pt}\right) C - \frac{R^S{}_{tot} k^S{}_{\text{int}} C}{K^S{}_{SS} + C} - \frac{V^M{}_{\max} C}{K^M{}_{SS} + C};$$

$$\frac{dA_T}{dt} = k_{pt} C V_c - k_{tp} A_T;$$

$$\frac{dR^S{}_{tot}}{dt} = k^S{}_{syn} - k^S{}_{\text{deg}} R^S{}_{tot} - \left(k^S{}_{\text{int}} - k^S{}_{\text{deg}}\right) \frac{R^S{}_{tot} C}{K^S{}_{SS} + C};$$

$$C_{tot}(0) = D_2 / V_c; \quad R^S{}_{tot}(0) = R^S{}_0 = k^S{}_{syn} / k^S{}_{\text{deg}}; \quad V^M{}_{\max} = R^M{}_0 k^M{}_{\text{int}}.$$

$$C = \frac{1}{2}\left[\left(C_{tot} - R^S{}_{tot} - K^S{}_{SS}\right) + \sqrt{\left(C_{tot} - R^S{}_{tot} - K^S{}_{SS}\right)^2 + 4 K^S{}_{SS} C_{tot}}\right]$$

Assumptions

- Drug-M-target complex elimination is fast, and total M-target concentration is constant. Therefore, MM approximation is valid;
- Drug-S-target complex elimination is slow, accumulation is significant. Therefore, QSS approximation should be used.

Limitations

Equations describe the drug that binds to only one target at a time. To describe drugs that bind to several targets simultaneously, the TMDD system needs to be modified to account for kinetics of all drug-multiple targets complexes.

Table 1 Model Parameters Used for Simulation

Parameter (Unit)	Explanation	Value	Comment
Linear part of the model [b]			
CL (L/day)	Linear clearance	0.3	Typical for fully-human therapeutic antibodies
V_c (L)	Central volume	3.0	
Q (L/Day)	Inter-compartment clearance	0.2	
V_p (L)	Peripheral volume	3.0	
F_{SC}	SC bioavailability	0.7	
k_a (1/day)	SC absorption rate constant	0.5	
Parameters of the S-target			
k^S_{on} (L/nmol/day)	Association constant	10	Within typical range
k^S_{off} (1/day)	Dissociation constant	0.1	
k^S_{int} (1/day)	Internalization rate	0.05	Similar to k_{el}
k^S_{syn} (nmol/L/day)	Syntheses rate	1	Consistent with literature data
k^S_{deg} (1/day)	Degradation rate	10	
R^S_0 (nmol/L)	*Baseline concentration*	*0.1* [a]	*$=k^S_{syn}/k^S_{deg}$*
K^S_{SS} (nmol/L)	*QSS constant*	*0.015* [a]	*$=(k^S_{off}+k^S_{int})/k^S_{on}$*
Parameters of the M-target			
k^M_{on} (L/nmol/day)	Association constant	5	Within typical range
k^M_{off} (1/day)	Dissociation constant	0.25	
k^M_{int} (1/day)	Internalization rate	15	Similar to k_{deg}
k^M_{syn} (nmol/L/day)	Syntheses rate	1.5	Consistent with literature data
k^M_{deg} (1/day)	Degradation rate	15	
R^M_0 (nmol/L)	*Baseline concentration*	*0.1* [a]	*$=k^M_{syn}/k^M_{deg}$*
V^M_{max} (nmol/L/day)	*Maximum elimination rate*	*1.5* [a]	*$=k^S_{syn}k^M_{int}/k^S_{deg}$*
K^M_{SS} (nmol/L)	*QSS constant*	*3.05* [a]	*$=(k^M_{off}+k^M_{int})/k^M_{on}$*

[a] *Derived parameters*; [b] Rate constants are: $k_{el}=CL/V_c$, $k_{pt}=Q/V_c$, $k_{tp}=Q/V_p$.

Table 2 Summary of Simulation Scenarios

Set	Models	Available data	BQL treatment	Parameter values
1	M1, M2, M3, M4	Free drug concentration; total S-target concentration	BQL values excluded	As in Table 1, i.e. $k^S_{syn}=1.0$, $k^M_{syn}=1.5$
2	M1, M2, M3		All values included	
3	M1, M2, M3	(Free drug+ drug-S-target complex) concentration; total S-target concentration	BQL values excluded	As in Table 1, i.e. $k^S_{syn}=1.0$, $k^M_{syn}=1.5$
4			All values included	
5	M1, M2, M3	Free drug concentration; total S-target concentration	BQL values excluded	As in Table 1 but $k^S_{syn}=0.5$, $k^M_{syn}=2.5$
6				As in Table 1 but $k^S_{syn}=2.5$, $k^M_{syn}=0.5$

Single-Subject Simulations

TMDD and QSS models were compared by simulation of free drug and total S-target concentration profiles for several sets of parameters and doses.

Population PK-PD simulations

- Typical Phase 1 – Phase 2 dataset was simulated using two-target full TMDD model:
  - ✓224 subjects following single or multiple-dose administration of 100 to 1000 nmol IV and SC doses;
  - ✓Rich data: 3250 free (unbound) or total (unbound and bound to S-target) drug concentrations and 3305 total (unbound and bound to the drug) S-target concentrations;
  - ✓Quantification limit of 0.1 or 0 nmol/L for drug and target data;
  - ✓Moderate (20% CV) inter-subject variability;
  - ✓Moderate (15-20% CV for drug and target data, respectively) residual variability;
- Four models were fitted to the data:
  - ✓M1: one-target QSS model – *ignored PK contribution of M-target*;
  - ✓M2: empirical combination of Michaelis-Menten (PK) and QSS (S-target) models - *ignored PK contribution of S-target*;
  - ✓M3: two-target QSS model;
  - ✓M4: full two-target TMDD model – *true model*;
- Two-sets of initial estimates: true (test 1) or randomly perturbed by 50-200% but within a reasonable range of parameters (test 2).
- Simulation and estimation were conduced using Nonmem 7® software;
- FOCEI was used for all estimation runs.

RESULTS

Single-subject simulations of the typical dosing regimens indicated that:

- ✓ In the typical range of parameters, the two-target TMDD and QSS models provide nearly identical description of the drug and target concentration data;
- ✓ Relative importance of two elimination routes (S- and M-targets) depends on the ratio k^S_{syn}/k^M_{syn} of their synthesis rates;

Population PK-PD simulations indicated that:

- ✓ Use of the full TMDD model was unfeasible (extremely long run times; instability of the model; dependence of the result on initial estimates; large bias in the binding parameter estimates);
- ✓ Two-target QSS model correctly estimated all model parameters and predicted decrease of unobserved M-target concentrations from baseline in all cases except when the M-target synthesis rate was significantly lower than the S-target synthesis. In this case, M-target parameter estimates were imprecise and biased;
- ✓ Two-target QSS model performed equally well when the total rather than free drug concentrations were available;
- ✓ Inclusion of concentrations below quantification limit (of 0.1 nmol/L) has not affected bias and precision of the parameter estimates;
- ✓ One-target QSS model that ignored contribution of the M-target performed well when the M-target contribution was indeed negligible but provided biased parameter estimates when this contribution was significant.

CONCLUSIONS

- ✓ The TMDD model and its approximation were derived for drugs that bind to more than one target;
- ✓ In the range of the parameters typical for the monoclonal antibody that binds soluble and membrane-bound forms of the target, QSS approximation of the TMDD model correctly describes drug and target concentrations;
- ✓ A simulation study demonstrated that QSS approximation of the two-target TMDD model provided unbiased and robust estimates of all relevant TMDD parameters.