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

Leonid Gibiansky, Ekaterina Gibiansky

QuantPharm LLC, North Potomac MD, USA (www.quantpharm.com)

QuantPharm

ABSTRACT

Purpose:

To develop an approach for description of pharmacokinetics for drugs with TMDD [1] that bind to S and M targets; to demonstrate on the simulated example that models based on the QSS approximation [2, 3] can identify parameters of both targets based on the free drug and total S-target concentrations.

Methods:

The TMDD equations were extended to describe drug interactions with multiple targets. The 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 bind to S and M targets. It was assumed that the unbound drug and 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:

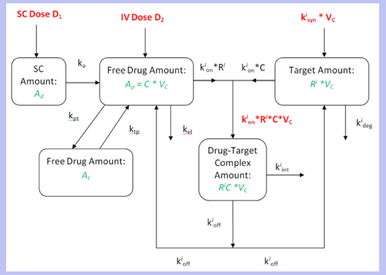
For the range of parameters typical for monoclonal antibodies with binding to S and M targets, S-target binding was described by the QSS approximation while Michaelis-Menten (MM) elimination term adequately described contribution of the M-target. Contributions of two targets could not be separated when 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 percent decrease from baseline for 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.

Schematic representation of the Multi-Target TMDD:

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



Two-Target (Soluble and Membrane) QSS Equations

$$\frac{dA_d}{dt} = -k_a A_d; \qquad A_d(0) = D_1$$

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

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

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

$$C_{tot}(0) = D_2 / V_c; \qquad R^S_{tot}(0) = R^S_0 = k^S_{syn} / k^S_{deg}; \qquad V^M_{max} = R^M_0 k^M_{int}.$$

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

Table 1 Model Parameters used for simulation of the Case Study

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 expressed as k_{el}=CL/V_c, k_{pt}=Q/V_c, k_{tp}=Q/V_p.

Assumptions

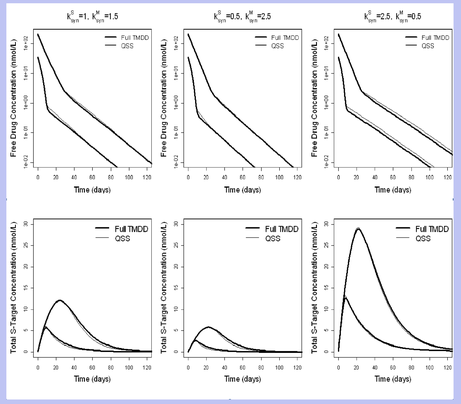
- Drug-M-target complex elimination is fast; total M-target concentration is constant; therefore, MM approximation is valid;
- Drug-S-target complex elimination is slow, accumulation is significant; therefore, QSS approximation should be used.

Limitations

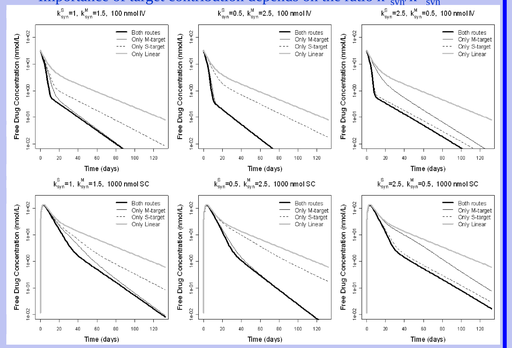
Equations describe the drug that binds to only one target at a time. To describe drugs that bind to several targets simultaneously, the TMDD system needs to be modified to account for kinetics of all drug-multiple targets complexes.

Single-Subject Simulations

The approximation is nearly identical to the full TMDD model



Importance of target contribution depends on the ratio k^S_{syn}/k^M_{syn}



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.

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

Table 3 Parameter Estimates (%RSE)[%Bias] of the Population Models M1-M4

Parameter	M1	M2	M3	M4 Test 1	M4 Test 2
CL	0.384 (2) [28]	0.286 (3) [5]	0.310 (2) [3]	0.299 (2) [0]	0.297 (2) [1]
V_c	3.07 (2) [2]	3.06 (2) [2]	2.95 (2) [2]	2.97 (2) [1]	2.98 (2) [1]
Q	0.127 (3) [37]	0.185 (2) [8]	0.200 (3) [0]	0.198 (2) [1]	0.196 (2) [2]
V_p	2.05 (3) [48]	3.13 (2) [4]	2.97 (3) [1]	2.97 (2) [1]	2.96 (2) [1]
F_{SC}	0.683 (2) [2]	0.679 (2) [2]	0.688 (2) [2]	0.683 (2) [2]	0.682 (2) [2]
k_a	0.559 (3) [12]	0.551 (3) [10]	0.52 3 (2) [5]	0.529 (3) [6]	0.532 (3) [6]
k^S_{on}	-	-	-	8.36 (4) [16]	6.43 (11) [36]
k^S_{off}	-	-	-	0.0952 (4) [5]	0.0728 (11) [27]
k^S_{int}	0.0649 (2) [30]	0.0546 (3) [9]	0.0529 (2) [6]	0.0495 (2) [1]	0.0489 (2) [2]
k^S_{syn}				1.01 (1) [1]	1.01 (2) [1]
k^S_{deg}	11.7 (3) [17]	9.00 (3) [10]	9.80 (3) [2]	9.19 (3) [8]	9.11 (3) [9]
R^S_0	0.0952 (2) [5]	0.110 (2) [10]	0.101 (2) [1]	0.110 [a] [10]	0.111 [a] [11]
K^S_{SS}	0.0081 (2) [46]	0.0106 (2) [31]	0.0107 (2) [29]	0.0173 [a] [12]	0.0189 [a] [13]
k^M_{on}	-	-	-	4.85 (6) [3]	1.82 (17) [64]
k^M_{off}	-	-	-	0.201 (11) [20]	0.0411 (42) [84]
k^M_{int}	-	-	-	7.62 (17) [49]	4.64 (5) [69]
k^M_{syn}	-	-	-	1.47 (4) [2]	1.50 (6) [0]
k^M_{deg}	-	-	-	12.8 (5) [15]	4.97 (18) [66]
V^M_{max}	-	2.71 (4) [81]	1.28 (8) [15]	0.88 [a] [41]	1.40 [a] [7]
K^M_{SS}	-	4.32 (4) [42]	2.57 (10) [16]	1.61 [a] [47]	2.57 [a] [16]
Objective function	16055	15781	15438	15197	15200

[a] Derived parameters; [b]CL, Q: clearance and inter-compartment clearance; V_c, V_p: central and peripheral volumes. Rate constants are expressed as k_{el}=CL/V_c, k_{pt}=Q/V_c, k_{tp}=Q/V_p.

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 approximations 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.

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