Target-Mediated Drug Disposition: New Derivation of the Michaelis-Menten Model, and Why It Is Often Sufficient for Description of Drugs with TMDD

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OBJECTIVES

- To derive the irreversible binding (IB) and IB Michaelis-Menten (MM-IB) approximations of the TMDD equations;
- To investigate parameter ranges where these approximations can be used for description of the TMDD data.

METHODS

- The IB approximation was derived assuming that the drug-target binding is irreversible.
- The MM-IB approximation was derived assuming that the free target concentration is much smaller than the drug concentration.
- A population PK dataset (3355 observations from 224 subjects) was simulated using the TMDD model and then estimated using the MM-IB approximation. Predicted drug concentrations were compared with the true (simulated) values. Bias and precision of the parameter estimates were investigated.

RESULTS

Irreversible Binding Equations

When binding is irreversible, $k_{off} = 0$. Then TMDD equations result in

$$\frac{dA_d}{dt} = -k_a A_d;$$

$$\frac{dC}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - k_{on} C \cdot R + k_{tp}\frac{A_T}{V};$$

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

$$\frac{dR}{dt} = k_{syn} - k_{deg} R - k_{on} C \cdot R;$$

C, R: concentrations of the free (unbound) drug and the target in the central compartment; k_{el}: elimination rate, k_{on}, k_{deg}, k_{int}, k_{syn}: binding, degradation, internalization, and the target production rate; V: central compartment volume; $R_0 = k_{syn}/k_{deg}$ is the baseline target concentration.

Irreversible Binding Quasi-Steady-State Equations

When k_{on} is large and assuming quasi-steady-state:

$$k_{syn} - k_{deg} R - k_{on} C \cdot R = 0 \quad \text{or} \quad R = \frac{R_0 K_{IB}}{K_{IB} + C} \quad \text{where} \quad K_{IB} = \frac{k_{deg}}{k_{on}}.$$

Then

$$\frac{dC_{dif}}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \left(k_{syn} - k_{deg} R\right) + k_{tp}\frac{A_T}{V};$$

$$C_{dif} = C - R = C - \frac{R_0 K_{IB}}{K_{IB} + C}; \qquad \frac{dC_{dif}}{dt} = \frac{dC}{dt}\left(1 + \frac{R_0 K_{IB}}{(C + K_{IB})^2}\right)$$

Therefore:

$$\frac{dC}{dt} = \frac{\frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}}{1 + \frac{R_0 K_{IB}}{(C + K_{IB})^2}}$$

Irreversible Binding Michaelis-Menten Equations

If $\frac{R_0 K_{IB}}{(C + K_{IB})^2} << 1$ then

$$\frac{dC}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}$$

These coincide with the Michaelis-Menten equations where

$V_{max} = k_{syn}$, $K_M = K_{IB}$.

RESULTS: Simulated PK Study

Target concentration << drug concentration

- Single-subject simulations of the typical dosing regimens using TMDD, IB, QSS-IB and MM-IB models indicated that all models would provide similar description of the PK data (Figure 1);
- Population PK model using QSS-IB approximation was able to recover the true (Table 1: true) model parameters (Table 1: QSS-IB) and correctly estimate the drug and target concentrations;
- Population PK model using MM-IB approximation was able to recover the true model parameters (Table 1: MM-IB) and describe the individual free drug concentration-time profiles;
- Estimate of KM parameter of the MM-IB model was much closer to the irreversible binding constant $KIB = k_{deg}/k_{on}$ than to the dissociation constant $K_D = k_{off}/k_{on}$ or quasi-steady-state constant $KSS = (k_{off} + k_{int})/k_{on}$ (Table 1)

Figure 1. Free drug and target concentrations

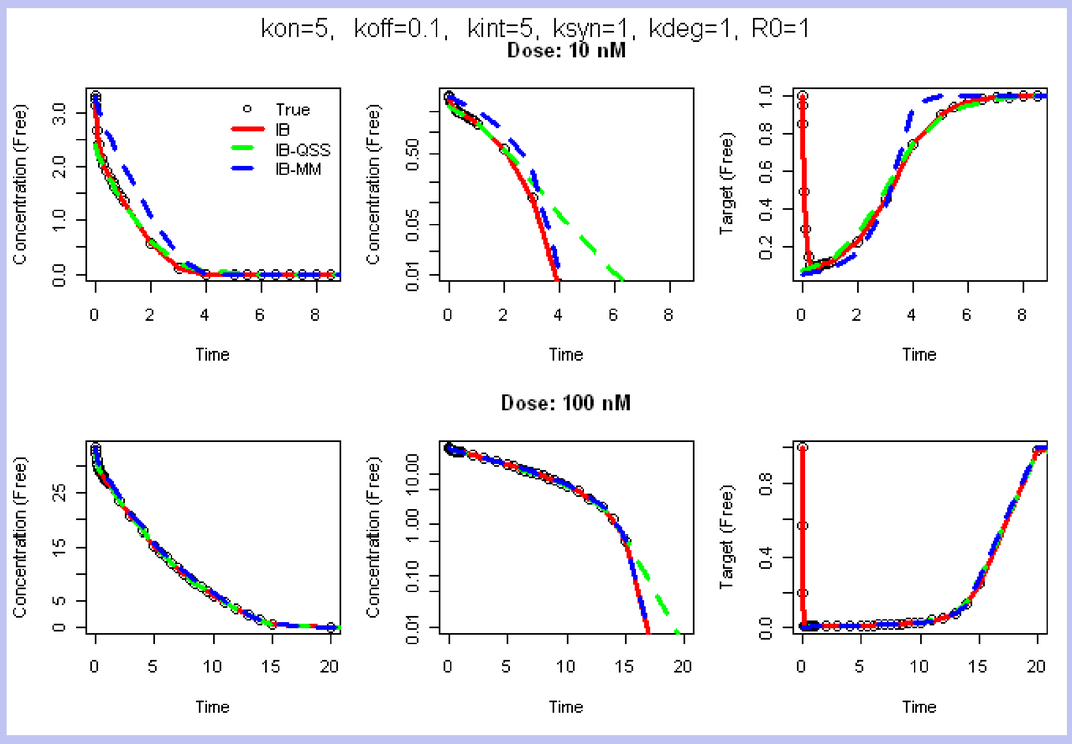

Table 1. Parameters of the true TMDD model and parameter estimates (%RSE) [%Bias] of the QSS-IB and MM-IB approximations

	Case 1: k_{on}=5, k_{off}=0.1, k_{int}=5, k_{syn}=1, k_{deg}=1			Case 2: k_{on}=5, k_{off}=1, k_{int}=10, k_{syn}=2, k_{deg}=1		
	True	QSS-IB	MM-IB	True	QSS-IB	MM-IB
CL	0.3	0.296 (2) [1]	0.299 (2) [0]	0.3	0.299 (2) [0]	0.306 (2) [2]
V_1	3.0	3.04 (2) [1]	3.02 (2) [1]	3.0	3.01 (2) [0]	2.97 (2) [1]
Q	0.2	0.197 (3) [1]	0.201 (2) [0]	0.2	0.201 (2) [0]	0.207 (2) [3]
V_2	3.0	2.97 (2) [1]	2.99 (2) [0]	3.0	3.01 (1) [0]	3.07 (1) [2]
F_{SC}	0.6	0.597 (2) [1]	0.598 (2) [0]	0.6	0.598 (1) [0]	0.602 (1) [0]
k_a	1.0	1.08 (3) [8]	0.975 (2) [3]	1.0	1.04 (3) [4]	0.891 (2) [11]
R_0	1.0	0.91 (19) [9]	-	2.0	1.34 (11) [33]	-
k_{syn}	1.0	1.01 (2) [1]	1.0 (2) [0]	2.0	2.01 (2) [0]	2.00 (2) [0]
K_{IB}	0.2	0.185 (4) [7]	0.206 (4) [3]	0.2	0.205 (2) [3]	0.215 (2) [7]
K_D	0.02			0.2		
K_{SS}	1.02			2.2		

CONCLUSIONS

- Irreversible binding limit of TMDD equations has been suggested. It is valid when the drug-target binding is irreversible, or when the internalization rate constant is much larger than the dissociation rate constant.
- The quasi-steady-state approximation of the irreversible binding equations has been suggested. It is valid when target concentration is at steady-state.
- It is shown that the Michaelis-Menten equation can be derived as an approximation of the irreversible binding equations. It is valid when the baseline target concentration is much smaller than the drug concentration.
- Relation between irreversible binding and Michaelis-Menten models explains why Michaelis-Menten model is often sufficient to describe pharmacokinetics of therapeutic monoclonal antibodies.