Title: Irreversible Binding (IB) and Michaelis-Menten (MM) Approximations of the Target-Mediated Drug Disposition (TMDD) Model.

Authors: Leonid Gibiansky, Ekaterina Gibiansky

Institutions: QuantPharm LLC, North Potomac MD, US

Purpose: To derive the IB and MM approximations of the TMDD equations; to investigate parameter ranges where these approximations can be used for description of TMDD data and for estimation of target production rate and free target suppression.

Methods: The IB approximation was derived assuming that the drug-target binding is irreversible. The MM 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. The MM approximation was used to describe the simulated data. Predicted drug concentrations were compared with the true (simulated) values. Bias and precision of the parameter estimates were investigated.

Results: The IB equations for a drug that is described by a two-compartment model and administered intravenously (D_2) and subcutaneously (D_1) are presented below:

$$\frac{dA_d}{dt} = -k_a A_d; \qquad C = \frac{1}{2}\left[C_{dif} - K_{IB} + \sqrt{\left(C_{dif} + K_{IB}\right)^2 + 4R_0 K_{IB}} \right]$$

$$\frac{dC_{dif}}{dt} = \frac{In(t) + k_a A_d}{V} - (k_{el} + k_{pt})C - \frac{k_{syn} C}{K_{IB} + C} + k_{tp}\frac{A_T}{V}; \qquad K_{IB} = \frac{k_{\deg}}{k_{on}};$$

$$\frac{dA_T}{dt} = k_{pt} C \cdot V - k_{tp} A_T; A_d(0) = D_1; C_{dif}(0) = D_2 / V - R_0; A_T(0) = 0.$$

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

The IB approximation is valid for high-affinity (large k_{on}) drugs in cases where the drug-target dissociation rate k_{off} is either small or much smaller than k_{int}. If $R_0<<C$, then $C_{dif}=C$ and the IB is described by the model with Michaelis-Menten elimination ($V_{max}=k_{syn}$, $K_M=K_{IB}$, $R_0=0$). A discrepancy between the true and MM solutions does not exceed R_0. In the simulation study for a system with $R_0<<C$, the MM model precisely estimated all relevant TMDD parameters with less than 5% bias and less than 5% relative standard error, and provided unbiased population and individual predictions of the unbound drug concentrations C and the target production rate k_{syn}.

Conclusions: The new IB and MM approximations of the TMDD equations were derived. The simulated examples demonstrated validity of these approximations and their ability to estimate the TMDD parameters. The results extend the parameter range where the Michaelis-Menten model can describe the TMDD data.