

Title: Numerical Testing of Assumptions for Target-Mediated Drug Disposition (TMDD) Equations: Why Inexact Model Provides Satisfactory Description?

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Background: TMDD equations are based on a number of assumptions such as: 1-to-1 drug-target binding; binding and elimination occur only in the central compartment; target R and drug-target complex RC do not distribute to the peripheral compartment; target production rate k_{syn} and degradation rate k_{deg} do not depend on the drug C or target R concentrations. The real biological systems are unlikely to conform to these assumptions. Yet the TMDD approximations were shown to provide excellent fit of the observed data.

Objectives: To investigate whether the classical TMDD model is able to describe simulated data from biological systems that violate the assumptions of the TMDD equations.

Methods: Dense population data of total drug $C_{\text{tot}}=C+RC$ and total target $R_{\text{tot}}=R+RC$ concentrations were simulated for the following TMDD models:

M1: standard;

M2: elimination from central and peripheral compartments;

M3: elimination only from the peripheral compartment;

M4: diffusion, binding, and internalization (k_{int}) of R and RC in both compartments;

M5: target production rate k_{syn} dependent on C or R;

M6: target production, binding and elimination in/from the peripheral compartment;

M7: 2 drug binding sites and various values of binding parameters k_{on} and k_{off} .

The quasi-steady state (QSS) approximation of the standard TMDD model was used to fit the data. Model predictions and parameter estimates were compared with true the values.

Results: The QSS approximation provided an excellent fit of the data for all models except M5, where R_{tot} predictions were biased at low R_{tot} values. Most parameter estimates agreed with the true values. The exceptions were (> 25% bias): parameters of the peripheral compartment (Q, V_2) were under-estimated in M2 and M3; clearance (CL) was under-estimated in M3; k_{int} was over-estimated in M4 and M6. CL, Q, V_2 , and k_{int} were biased in M5 but the fit was improved and bias eliminated when dependencies $k_{\text{syn}}(C)$ or $k_{\text{syn}}(R)$ were added. QSS constant K_{SS} was in the range of 40%-103% of the true $(k_{\text{off}}+k_{\text{int}})/k_{\text{on}}$ value in M7.

Conclusions: QSS approximation of the standard TMDD model can be used to describe TMDD system even if underlying assumptions are not met by the true system. The fit was most sensitive to perturbations of the target production rate.