OBJECTIVES

The data were simulated from the full TMDD models M1-M6 and estimated using the QSS approximation of model M1. Red: bias exceeds 25%.

TMDD equations [1] contain many assumptions that are unlikely to hold in real biological systems, such as:

- One-to-one drug-target binding;
- Binding and elimination occur only in the central compartment;
- Free target (R) and drug-target complex (RC) do not diffuse to the peripheral compartment;
- Target production rate (ksyn) and degradation rate (kdeg) do not depend on the drug (C) or target concentrations.

Yet TMDD approximations often provide an excellent fit of observed data. We aim to investigate whether the classical TMDD model can describe the data simulated from the biological systems that violate the assumptions of TMDD equations.

METHODS

Dense population data, concentrations of the total drug (Ctot=C+RC) and the total target (Rtot=R+RC) were simulated for the following TMDD models:

- M1: standard two-compartment TMDD model with target production, one-to-one binding, and elimination in the central compartment only [1];
- M2: elimination from the central and peripheral compartments;
- M3: elimination only from the central compartment;
- M4: R and RC diffusion to the peripheral compartment, and binding and internalization (kint) in both compartments;
- M5: ksyn dependent on C or R;
- M6: Target production, binding and elimination from the peripheral compartment;
- M7: Two drug binding sites with various combinations of binding parameters koff and kon.

The quasi-steady state (QSS) approximation of the standard TMDD model [2] was used to fit the data. Model predictions and parameter estimates were compared with true values.

RESULTS

- The QSS approximation provided an excellent fit of the data for models M1-M7 except M5, where Rref predictions were biased at low Rref values.
- Most parameter estimates agreed with the true values. The exceptions were (> 25% bias):
  - Parameters of the peripheral compartment (Q,Vp) were under-estimated in M2 and M3;
  - Clearance (CL) was under-estimated in M3;
  - koff was over-estimated in M4 and M6;
  - CL, Q, Vp, and koff were biased in M5 but the fit was improved and bias eliminated when dependencies koff(C) or koff(R) were added.
- Investigation of the systems with 1:2 binding (antibody with two binding sites) indicated that the concentrations of the total drug and the total target were well described by the QSS approximation of the standard TMDD model.
- The parameter estimates of model M7 were unbiased with the exception of QSS constant Kss that was in the range of 40%-103% of the true (koff+kint)/kon value.

CONCLUSIONS

- The QSS approximation of the standard TMDD model provides an excellent fit even when underlying assumptions are violated but the parameter estimates may not correspond to the true values. The fit was most sensitive to perturbations of the target production rate.
- Central compartment measurements do not allow to determine true structural model of the system with TMDD.

REFERENCES