Target-Mediated Drug Disposition (TMDD): Indirect-Response Models Can Be Used to Estimate Unobservable Unbound Target Concentrations

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Purpose.

To derive relationships between the parameters of TMDD and indirect response models (IRM); using population PK-PD data simulated from a TMDD model, demonstrate that IRM can be used to estimate TMDD parameters and unobservable unbound target concentrations.

Methods.

TMDD equations and its quasi-steady-state (QSS) approximation were used to derive the IRM equations for total target concentrations. The ability of IRM to estimate the TMDD parameters and predict unobservable unbound target concentrations were investigated using population PK-PD simulations in NONMEM6. The dataset included rich data from two studies. Study 1 included 4 cohorts of six subjects administered single 100 nmol IV, 300 nmol SC, 1000 nmol IV, or 3000 nmol SC doses. Study 2 included two 100-subject arms administered multiple 1000 or 3000 nmol SC doses at 4 week intervals. PK parameters of the simulation model were typical for monoclonal antibodies. TMDD binding and target turnover parameters were similar to those estimated for omalizumab with the elimination rate of the drug-target complex (k_{int}) 5 times lower than the elimination rate of the unbound target (k_{deg}). Unbound drug and total target concentrations were simulated from the TMDD model. The QSS approximation and IRM were used for estimation.

Results.

Direct correspondence between the parameters of the TMDD and IRM was established. This correspondence allows estimating TMDD parameters (production and degradation rate constants of the unbound target, quasi-steady state constant, and degradation rate constant of the drug-target complex) and unobservable unbound target concentrations from estimated IRM parameters. In the simulation, IRM precisely estimated the TMDD population parameters with less than 7% bias and less than 5% relative standard error, and provided unbiased population and individual predictions of the total and unbound target concentrations.

Conclusion.

The equation for the total target concentration of the QSS approximation coincides with the indirect-response model with inhibition (when $k_{deg} > k_{int}$) or stimulation (when $k_{int} > k_{deg}$) of elimination. The simulated population PK-PD study demonstrated that for drugs with TMDD, IRM are in fact mechanistic models that can be used to estimate TMDD model parameters and unobservable unbound target concentrations that are important for pharmacodynamic modeling.

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