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PAGE. Abstracts of the Annual Meeting of the Population Approach Group in Europe.
ISSN 1871-6032

Reference:
PAGE 19 (2010) Abstr 1728 [www.page-meeting.org/?abstract=1728]

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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Poster: Methodology- Other topics

Purpose: To derive the Irreversible Binding (IB) and Michaelis-Menten (MM) approximations of the Target-Mediated Drug Disposition (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 (i) the drug-target binding is irreversible and (ii) the free target concentration is in quasi-steady-state. Further, 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 full TMDD model. The MM approximation was used to describe the simulated data. Predicted drug concentrations were compared with the true 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 as intravenous bolus (D_2), intravenous infusion ($In(t)$) and subcutaneous (D_1) doses are presented below:

$dA_d/dt = -k_a A_d$,
$A_d(0) = D_1$,
$dC_{dif}/dt = [In(t) + k_a A_d]/V - (k_{el} + k_{pt})C - k_{syn} C/(K_{IB} + C) + k_{tp} A_T/V$,
$C_{dif}(0) = D_2/V - R_0$,
$dA_T/dt = k_{pt} C V - k_{tp} A_T$,
$A_T(0) = 0$,
$C = 0.5 \{C_{dif} - K_{IB} + [(C_{dif} + K_{IB})^2 + 4 R_0 K_{IB}]^{1/2}\}$,
$K_{IB} = k_{deg}/k_{on}$

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}. This is typical for the therapeutic monoclonal antibodies with membrane-bound targets. If R_0 is much smaller than C then $C_{dif} = C$ and the irreversible binding equations are equivalent to the model with the Michaelis-Menten elimination ($V_{max} = k_{syn}$, $K_M = K_{IB}$, $R_0 = 0$). The discrepancy between the true and MM solutions does not exceed R_0. In the simulation study for a system with R_0 significantly smaller than C, the MM model precisely estimated all relevant TMDD parameters 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 describes the TMDD data.

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