The Relationship between Target-Mediated Drug Disposition (TMDD) and Models with Time-Dependent Clearance

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METHODS/RESULTS (continuation)

Substituting expressions for the concentration of target cells in the equation for $A_1$, one can arrive at the equation

$$\frac{dA_1}{dt} = \left(\frac{CL_{ss}}{V_c} + \frac{Q}{V_p} + \frac{A_2}{V_c} \cdot k_{int} A_i R_i \right) - k_{deg} A_i R_i \cdot A_1(0) = D_{iv};$$

Here target-mediated elimination $k_{int} A_i R_i \cdot A_1$ is proportional to the drug amount $A_i$, the target cell concentration $R_i$, and internalization rate $k_{int}$ that may depend on drug-target binding rate $k_{syn}$, density and turnover of target receptors. Target cells are in equilibrium prior to drug administration; kill rate of target cells can be described by Emax function of drug concentrations $k_{int} A_i R_i / (IC_{50} + C)$.

If $IC_{50}$ is significantly lower than trough concentration $C_{min}$, then one can derive equation

$$\frac{dR}{dt} = k_{syn} - (k_{deg} + k_{kill}) R_i; \quad t > 0; \quad R(0) = R_0 = k_{syn} / k_{deg}, \quad \text{that has a solution} \quad R = R_0 \left( \frac{k_{deg} + k_{kill}}{k_{deg} + k_{kill}} e^{-(k_{deg} + k_{kill}) t} \right); \quad t > 0.$$

REFERENCES


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