Dose Correction for the Michaelis-Menten Approximation of the Target - mediated Drug Disposition Model

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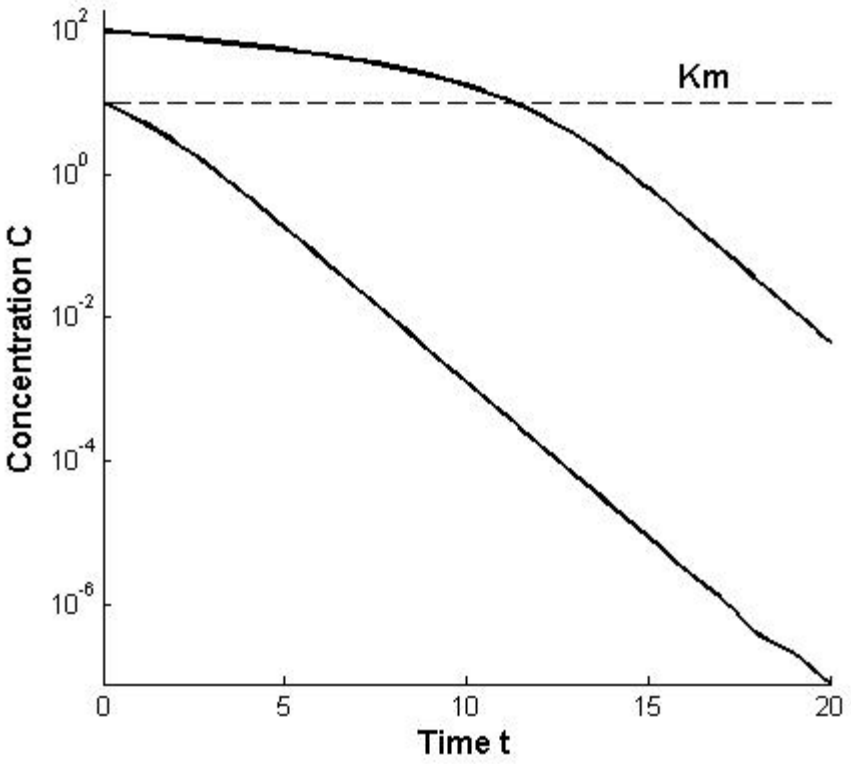
Michaelis-Menten Elimination Rate



$$V\frac{dC}{dt} = -\frac{V_{max}C}{K_m + C}$$

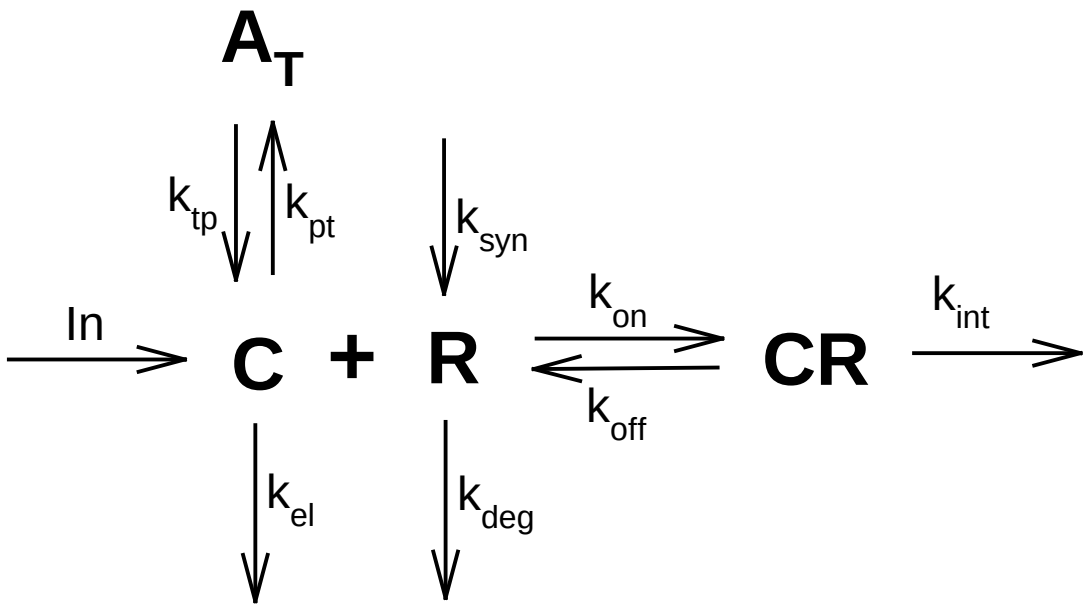
$$C(0) = \frac{Dose}{V}$$

V_{max} = maximum elimination rate constant.

K_m = Michealis-Menten constant

Clearance saturation: If C >> K_m the concentration vs. time plateaus

Target Mediated Drug Disposition PK Model



$$dC/dt = In(t) - k_{on} \cdot R \cdot C + k_{off} \cdot CR - (k_{el} + k_{pt}) \cdot C + k_{tp} \cdot A_T / V_c$$

$$dA_T/dt = k_{pt} \cdot C \cdot V_c - k_{tp} \cdot A_T$$

$$dR/dt = k_{syn} - k_{on} \cdot R \cdot C + k_{off} \cdot CR - k_{deg} \cdot R$$

$$dCR/dt = k_{on} \cdot R \cdot C - (k_{off} + k_{int}) \cdot CR$$

Mager and Jusko. J Pharmacokinet Pharmacodyn. 28:507-32 (2001)

Rapid Binding TMDD PK Model

Equilibrium assumption: Binding of free drug to its target is rapid, so that drug and receptor are in dynamic equilibrium

$$\frac{R \cdot C}{CR} = \frac{k_{off}}{k_{on}} \equiv K_D$$

$C_{tot} = C + CR$ and $R_{tot} = R + CR$

$$dC_{tot}/dt = In(t) - k_{int} \cdot C_{tot} - (k_{el} + k_{pt} - k_{int}) \cdot C + k_{tp} \cdot A_T / V_c$$

$$dA_T/dt = k_{pt} \cdot C \cdot V_c - k_{tp} \cdot A_T$$

$$dR_{tot}/dt = k_{syn} - (k_{int} - k_{deg}) \cdot (C_{tot} - C) - k_{deg} \cdot R_{tot}$$

$$C = 1/2 \left[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4 \cdot K_D \cdot C_{tot}} \right]$$

where C is a solution of the equilibrium equation

Mager and Krzyzanski, Pharm. Res. (2005).

Michaelis-Menten Approximation of RB TMDD Model

If R_{tot} = constant:

$$\frac{dC}{dt} = \frac{In(t) - \frac{k_{int} R_{tot} C}{K_D + C} - (k_{el} + k_{pt})C + k_{tp} A_T / V_c}{1 + \frac{R_{tot} K_D}{(K_D + C)^2}}$$

Wagner, 1971

If $R_{tot} << K_D$ or $C << K_D$:

$$\frac{R_{tot} K_D}{(K_D + C)^2} << 1$$

Michalelis- Menten approximation:

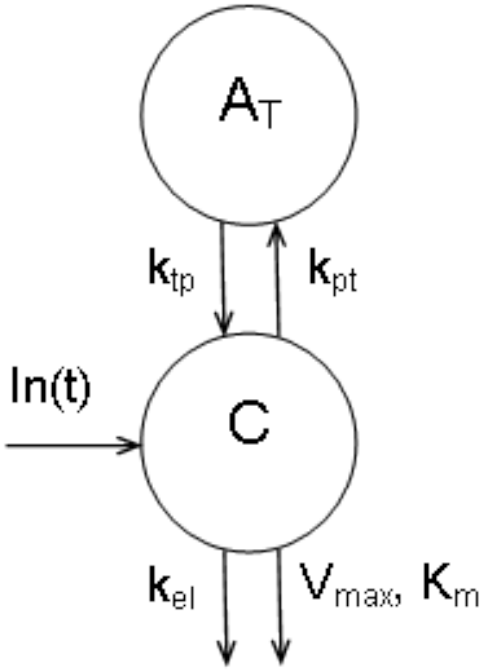
$$\frac{dC}{dt} = In(t) - \frac{k_{int} R_{tot} C}{K_D + C} - (k_{el} + k_{pt})C + k_{tp} A_T / V_c$$

$$V_{max} = k_{int} R_{tot} V_c \qquad K_m = K_D$$

J. G. Wagner, Biopharmaceutics and Relevant Pharmacokinetics (1971)

Yan and Krzyzanski, JPKPD 37:25 (2010).

M-M TMDD Model



$$\frac{dC}{dt} = -\frac{(V_{max}/V)C}{K_m + C} - (k_{pt} + k_{el})C + k_{tp}A_T/V$$

$$\frac{dA_T}{dt} = k_{pt}CV - k_{tp}A_T$$

$$C(0) = \frac{Dose}{V}$$

$$A_T(0) = 0$$

The initial condition for IV bolus dose is Dose/V.
The initial concentration for RB TMDD model C(0) ≠ Dose/V

Yan and Krzyzanski, JPKPD 37:25 (2010).

Correct Initial Condition for M-M Model

Initial condition based on RB TMDD model:

$$C_{corr}(0) = \frac{1}{2}\left[\frac{Dose}{V} - R_{tot0} - K_D + \sqrt{\left(\frac{Dose}{V} - R_{tot0} - K_D\right)^2 + 4K_D\frac{Dose}{V}}\right]$$

IV bolus dose needs to be corrected by amount bound to receptors:

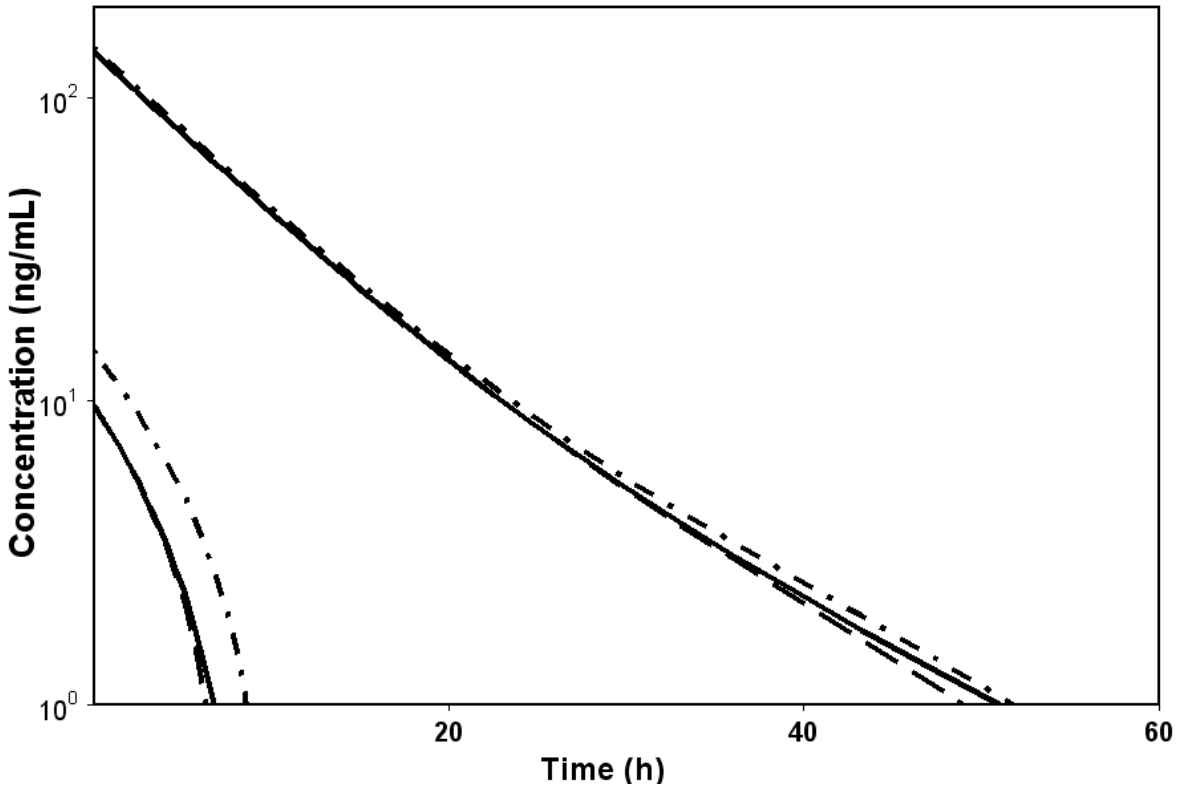
$$C_{corr}(0) = \frac{Dose}{V} - \frac{R_{tot0}C_{corr}(0)}{K_D + C_{corr}(0)}$$

Correction introduces k_{int} into M-M model:

$$C_{corr}(0) = \frac{1}{2}\left[\frac{Dose}{V} - \frac{V_{max}}{k_{int}V} - K_m + \sqrt{\left(\frac{Dose}{V} - \frac{V_{max}}{k_{int}V} - K_m\right)^2 + 4K_m\frac{Dose}{V}}\right]$$

Yan and Krzyzanski, JPKPD (2012) (accepted).

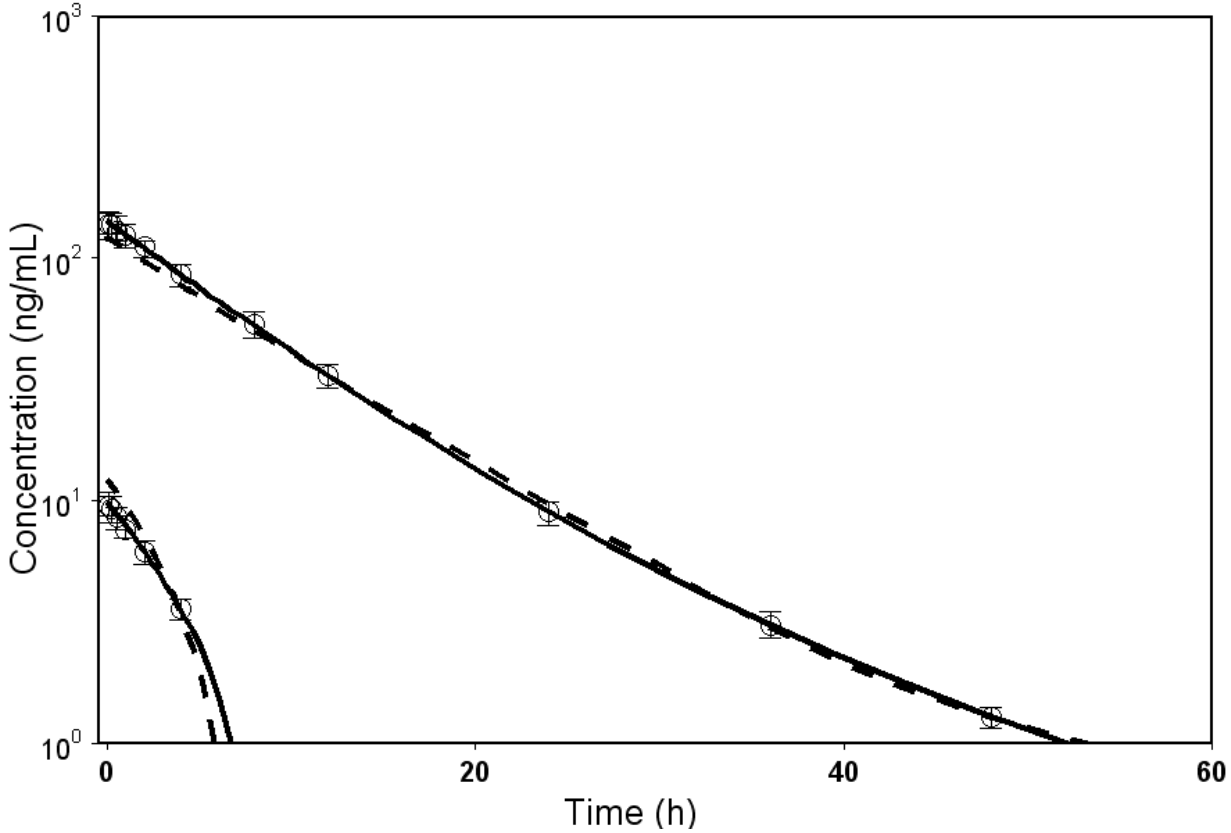
Impact of Dose Correction on PK Profile



Simulation of the pharmacokinetic profile with IV bolus doses using the RB TMDD model (solid line), M-M model with corrected initials (dash line), and M-M model with uncorrected initials (dash-dot line).

Yan and Krzyzanski, JPKPD (2012) (accepted).

Bias of Parameter Estimates of M-M TMDD Model



Simulated PK data fitted with the original and corrected M-M models. Open circle represents simulated median data from 100 replicates. Error bar represents the interquartile range. Model predictions are shown for the corrected M-M model (solid lines) and original M-M model (dashed lines).

Yan and Krzyzanski, JPKPD (2012) (accepted).

Parameter Estimates

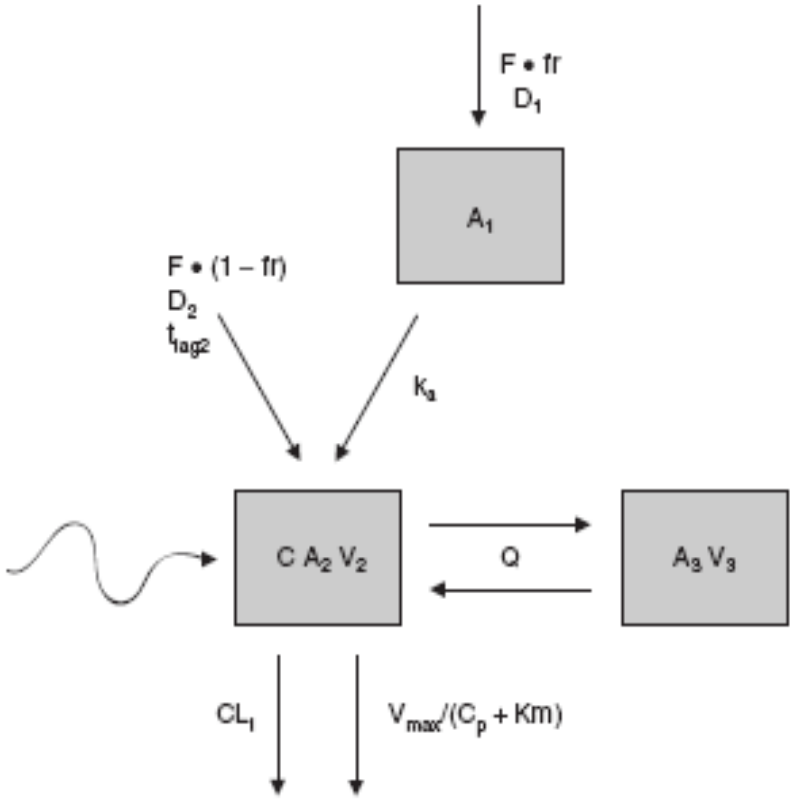
Parameter	Estimate (IQR)			Parameter bias (%)	
	True value	Original M-M	Corrected M-M	Original M-M	Corrected M-M
k_{el} (h^{-1})	0.0382	0.00143 (0.0003, 0.00386)	0.0423 (0.0147, 0.0725)	-96.2	10.6
V_c (mL kg^{-1})	68.3	81.9 (78.7, 84.8)	68.3 (64.6, 72.3)	20	0.027
k_{cp} (h^{-1})	0.0806	0.0979 (0.0918, 0.105)	0.078 (0.0594, 0.0962)	21.4	-3.24
k_{pc} (h^{-1})	0.0148	0.0224 (0.0194, 0.0258)	0.0157 (0.0115, 0.0254)	51	5.75
k_{int} (h^{-1})	0.173	N/A	0.167 (0.107, 0.223)	N/A	-3.64
k_{deg} (h^{-1})	0.173[a]	N/A	N/A	N/A	N/A
K_{eq} (ng mL^{-1})	0.131	N/A	N/A	N/A	N/A
R_{tot0} (ng mL^{-1})	5	N/A	N/A	N/A	N/A
V_{max} (ng kg^{-1} h^{-1})	59.1[b]	144.5 (122.2, 157.7)	56.9 (43.8, 72.1)	145	-3.7
K_m (ng mL^{-1})	0.131[c]	1.06 (0.616, 1.3)	0.29 (0.0685, 0.664)	711	121
WSSR	N/A	0.567 (0.436, 0.748)	0.243 (0.173, 0.321)	N/A	N/A
AIC	N/A	2.63 (-2.11, 7.07)	-10.0 (-15.8, -5.32)	N/A	N/A

[a] Fixed at k_{int} value. [b] Calculated as $R_{tot0}k_{int}V$. [c] Same to K_D. IQR, interquartile range. N/A, not applicable.

Yan and Krzyzanski, JPKPD (2012) (accepted).

Population Pharmacokinetics Meta-Analysis of Recombinant Human Erythropoietin in Healthy Subjects

Per Olsson-Gisleskog,[1] *Philippe Jacqmin*[1] and *Juan Jose Perez-Ruixo*[2]



$$\frac{dA_1}{dt} = \begin{cases} \frac{\text{Dose} \bullet \text{fr} \bullet F}{D_1} - k_a A_1, & \text{if } t \le D_1 \\ -k_a A_1, & \text{if } t > D_1 \end{cases}$$

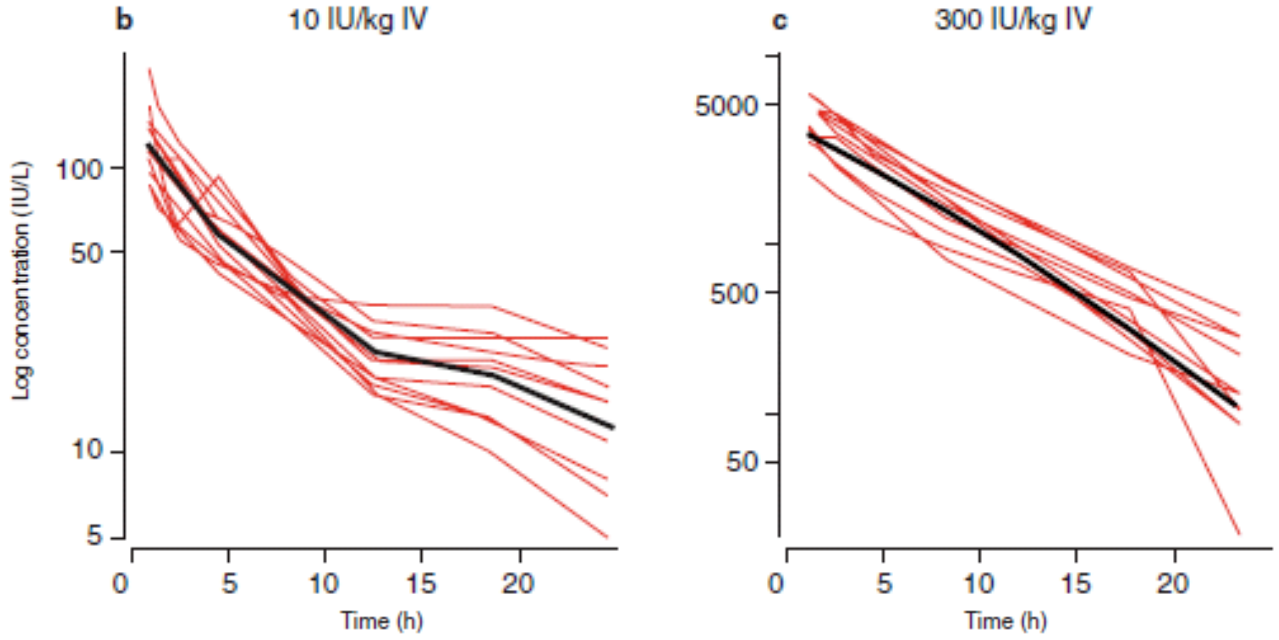
$$\frac{dA_2}{dt} = \begin{cases} \frac{\text{Dose} \bullet (1 - \text{fr}) \bullet F}{D_2} + k_a A_1 + k_{32} A_3 - k_{23} A_2 - k_{20} A_2 - \frac{V_{max} A_2 / V_2}{Km + A_2 / V_2}, & \text{if } t_{lag2} \le t \le D_2 \\ k_a A_1 + k_{32} A_3 - k_{23} A_2 - k_{20} A_2 - \frac{V_{max} A_2 / V_2}{Km + A_2 / V_2}, & \text{if } t < t_{lag2} \text{ or } t > D_2 \end{cases}$$

Olsson-Gisleskog et al. Clin. Pharmacokinet. 46:159 (2007).

Correction Factor for Lower Dose EPO Concentrations

$$C = F_{iv} \frac{A_2}{V_2}$$

$$C = \frac{A_2}{V_2}$$



Relative exposure at the two lowest intravenous dose levels, 10 IU/kg and 20 IU/kg, was found to be significantly lower than at higher dose levels. This was best fitted in the model by using a correction factor for these doses.

Parameter	Estimate	RSE (%)
F_{iv}, dose ≤20 IU/kg (%)	60.0	7

Olsson-Gisleskog et al. Clin. Pharmacokinet. 46:159 (2007).

Conclusions

- Correction of the initial dose the M-M approximation of the TMDD model is necessary due to fraction of dose bound to the receptors.
- Correction is significant for lower doses and negligible for larger doses.
- Inclusion of the correction introduces k_{int} parameter into M-M model.
- Lack of correction biases parameter estimates.
- Further studies are necessary to investigate the impact of the correction on multiple IV bolus data .
- Correcting doses for other routes of administration remains unclear.

Acknowledgments

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