Implications for animal-human scaling of the parallel elimination profile PK model

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Background and Objective

Translation/scaling of PK-PD models can aide in dose selection for first-in-human and proof of mechanism/concept studies. The intent is to predict concentrations at the effect site and their effects in humans from animal PK-PD information. Effect site concentrations are often immeasurable in humans, however, and assumptions are necessary for the prediction of these. The animal PK model can inform these assumptions. Equilibration between the effect site and central compartments might suggest scaling/predicting based on the central compartment. If the central and effect site compartments have dissimilar profiles, then the effect site concentration might be considered. If the concentration profiles are not in equilibration, but have parallel elimination rates (the central-effect site rate constants are inestimable – likely due to the study design), a parallel elimination profile (PEP) PK model can be utilized. This work introduces the PEP model and details the issues associated with scaling (and applying) it.

Methods

A 2-compartment model (Figure 1) was fitted initially and found

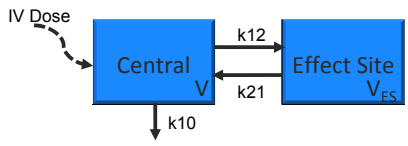

Figure 1. *Pictorial description of a 2-compartment model following an IV bolus dose.*

unstable. The estimate of k21 was 10.5 1/h (≈4 minute half-life) while k12 was estimated to be 0.344 1/h. Plots indicated that the central and effect site demonstrated parallel elimination (profiles) with only one log-linear phase. These observations led to postulating and deriving the PEP model. The model is derived under the limiting condition of $k_{21}\rightarrow\infty$ as follows and is depicted graphically in Figure 2.

$$(1)\quad \lim_{k_{21}\to\infty} C = \lim_{k_{21}\to\infty}\left\{\frac{D}{V(\beta-\alpha)}\left[(k_{21}-\alpha)\exp(-\alpha t)-(k_{21}-\beta)\exp(-\beta t)\right]\right\} = \frac{D}{V}\exp(-k_{10}t)$$

Noting that the $\lim[k_{21}/(\beta-\alpha)]= -1$ and letting $V_{ES}\cdot k_{21} = c$ yields

$$(2)\quad \lim_{k_{21}\to\infty} C_{ES} = \lim_{k_{21}\to\infty}\left\{\frac{D\cdot k_{12}}{V_{ES}(\beta-\alpha)}\left[\exp(-\alpha t)-\exp(-\beta t)\right]\right\} = \frac{D\cdot k_{12}}{c}\lim_{k_{21}\to\infty}\left\{\frac{k_{21}}{(\beta-\alpha)}\right\}\lim_{k_{21}\to\infty}\left\{\left[\exp(-\alpha t)-\exp(-\beta t)\right]\right\} = \frac{D\cdot k_{12}}{c\cdot(-1)}\left[0-\exp(-k_{10}t)\right] = \frac{D}{V_{ES}^{*}}\exp(-k_{10}t),\quad V_{ES}^{*}=\frac{c}{k_{12}}$$

Note that $V_{ES}\neq V_{ES}^{*}$, V_{ES} is the 2 compartment model volume.

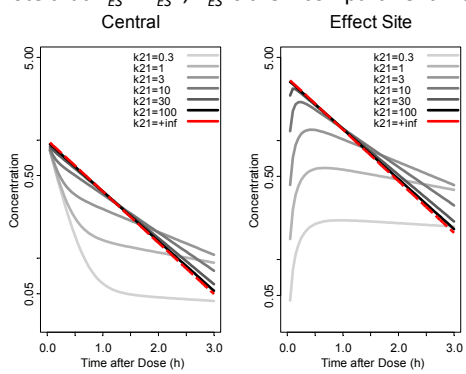

Figure 2. *Simulation demonstrating the convergence of the central and effect site kinetics to 1 compartment kinetics with identical elimination profiles but differing volumes.*

Results

The PEP model fit the data adequately (see Figure 3). The central

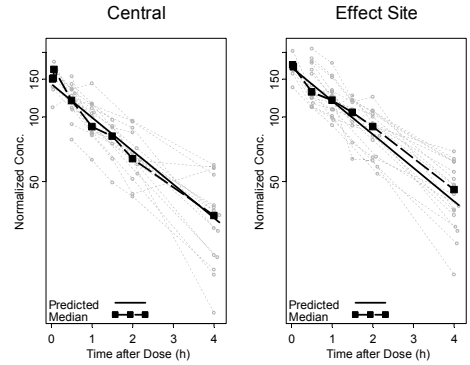

Figure 3. *Observed and PEP model predicted (typical individual) concentrations for the central and effect site compartments from a case study.*

(effect site) residual variance estimate was 12.9% (11.0%), corroborating the 2 compartment model overparameterization (the estimates are near assay error and are identical to the unstable 2 compartment model estimate – Figure 1). The V_{ES}* estimate was 16.4% (4.8% SE) less than V, fitting the central and effect site compartments simultaneously. A likelihood ratio test for $V = V_{ES}$* yielded a ΔOFV =9.278, substantiated by the confidence interval (16.4 − 2·4.8 >0). This statistical test rejected rapid equilibration ($Q\rightarrow\infty$) between the two compartments.

Note, $V_{ES}\cdot k_{21}=c$ implies a small effect site volume. Also, $V_{ES}\cdot k_{21} = c \neq V\cdot k_{12}$, which violates the standard steady state assumption. Otherwise Eqs. (1) -(2) yield *identical* kinetic models, which implies rapid equilibration. For 2 compartment linear models, $\int C_{ES}\cdot dt = \int C\cdot dt$ (0-∞), however for the PEP model, $\int C_{ES}\cdot dt \neq \int C\cdot dt$ (0-∞), perhaps an unappealing theoretical result. *Nevertheless, the PEP model provides a parsimonious fit to the data and yields accurate central and effect site concentration predictions.*

Discussion/Conclusion

The analytical derivation indicates that the PEP V_{ES}* estimate is influenced by the unidentifiable k_{12} parameter (it is an apparent volume). This implies that effect site predictions using typical scaling procedures on V_{ES}* are likely to be inaccurate. Therefore, other pharmacological considerations or assumptions might be necessary to improve the accuracy of the predictions and provide suitable utility for dose selection or decision making when designing proof of concept studies.

The study design (Figure 3) is likely the major factor in not identifying a 2 compartment model. Therefore, whenever the effect site is immeasurable in humans, experimentalists might consider a more dense set of nominal times in animals to ensure identifiability of the inter-compartment rate constants, and the volumes associated with these.

Appendix

Other more typical limiting kinetic models (limits of model in Figure 1):

Rapid Equilibration

$$(3)\ \lim_{Q\to\infty} C = \frac{D}{V+V_{ES}}\exp\left(-\frac{CL}{V+V_{ES}}t\right)$$

$$(4)\ \lim_{Q\to\infty} C_{ES} = \frac{D}{V+V_{ES}}\exp\left(-\frac{CL}{V+V_{ES}}t\right)$$

keo – effect site link

$$(5)\ \lim_{k_{12}\to 0} C = \frac{D}{V}\exp(-k_{10}t)$$

$$(6)\ \lim_{k_{12}\to 0} C_{ES} = \frac{D\cdot k_{21}}{V(k_{21}-k_{10})}\left[\exp(-k_{10}t)-\exp(-k_{21}t)\right]$$

$$k_{21}\cdot V_{ES} = k_{12}\cdot V \quad (k_{eo}\equiv k_{21})$$

References

1. M Gibaldi and D Perrier. *Pharmacokinetics*. Marcel Dekker, Inc. New York, NY (1982)