

Title: Cross-Species Scaling of CNS A β 40 Response to a Gamma Secretase Inhibitor Through Semi-Mechanistic PK/PD Modeling and Application to Early Decision Making

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Objectives: The amyloid hypothesis contends that build-up of A β and its associated plaques in brain tissue leads to development Alzheimer's disease. The γ -secretase inhibitor, MK-0752, can acutely and significantly lower CSF A β 40 concentrations in humans [1]. The objectives of this work were to develop PK/PD models of CNS A β 40 response to MK-0752 in 5 different species (3 rodent, monkey, and human) and to develop methods for cross-species scaling of the PK/PD relationship.

Methods: Data were obtained as follows: In the rodents (Tg-mouse, YAC-mouse, and guinea pig) brain tissue and plasma were obtained at approximately 4 hours post-dose and analyzed for A β 40 and MK-0752 concentrations. In CMP-ported rhesus monkeys serial plasma and CSF samples were obtained following single-dose administration and were analyzed for A β 40 and MK-0752 concentrations. In human clinical studies, serial plasma and CSF samples were obtained in healthy subject over 12-30 hours following a single dose through a lumbar spine catheter. Inconsistencies in the presence or absence of time delays between PK and PD endpoints dictated differing PK/PD model structures across the species, but the core equation for impact of MK-0752 on brain A β was kept consistent across all models. The IC50 values from this relationship varied considerably across the species in a manner consistent with differences in plasma protein binding. Therefore, a cross-species scaling approach incorporating a plasma protein binding correction was developed. All models and simulations were conducted using ASCL software (AEgis) and utilized naïve pooling approaches to obtain mean parameter estimates.

Results: Data in the 3 rodent species were well described by a sigmoid Emax relationship. The parameter estimates are provided in Table 1. Data from the monkey were also well described by a sigmoid Emax

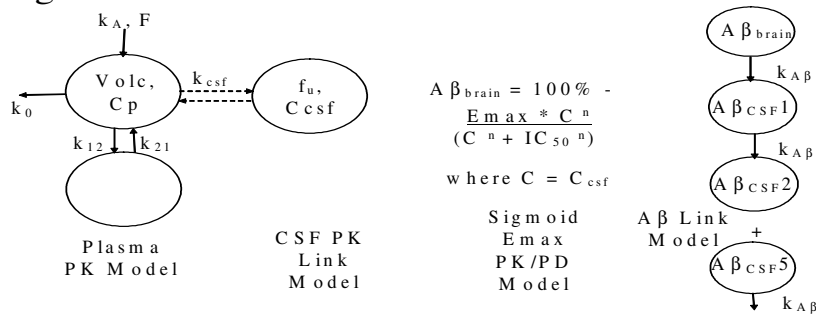
relationship and the serial sampling allowed for confirmation of minimal hysteresis in this species. Across the 4 non-human species, there was reasonable agreement on the estimates for Emax and the hill coefficient; however there was a ~20-fold variation in IC50 estimates, that may have been related to protein binding differences.

Table 1.
Fit PK/PD Model Parameter Values Across Species

Species	Model Parameter Estimate			Plasma Free Fraction
	IC50 (μ M)	Emax (% reduction)	n	
MK-0752 plasma conc / brain A β level				
Tg mouse	0.57	82.0	1.17	0.036
YAC mouse	1.96	72.4	1.14	0.031
Guinea Pig	2.06	79.7	1.08	0.040
MK-0752 plasma conc / CSF A β level				
Monkey	12.07	90.1	2.04	0.0043
Human	22.3	63.0	4	0.0061

In humans, a substantial time-delay was noted between peak drug concentrations in CSF (3-4 hr) and peak A β reduction in CSF (~12 hr) and application of the sigmoid Emax model used in animals was judged inappropriate. A semi-mechanistic PK/PD model was developed that incorporated time delay in drug reaching the CNS and in the brain A β response reaching the location of lumbar CSF sampling as diagrammed in Figure 1. This model well described the plasma and CSF PK data and the CSF A β data and produced the dose and time-dependent variations in the 4 analytes/anatomical sites tracked, consistent with the data. Because the model kept the core sigmoid Emax equation to describe drug effects on brain A β response, the parameters from this model could still be compared to those obtained in animals as shown in Table 1.

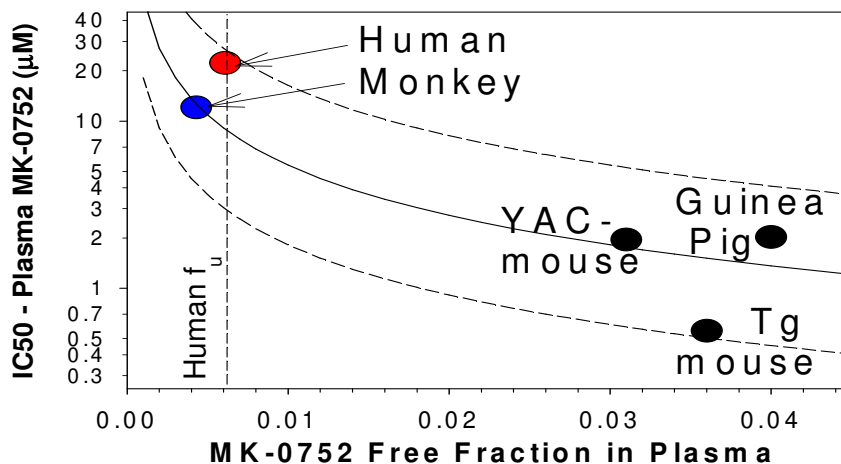
Figure 1. Semi-mechanistic Human PK/PD Model



A scaling approach was developed to related IC50 across species utilizing a protein binding correction, that assumed that the equivalent free IC50 values would be similar across all species (IC50 = 0.055 / fu). As shown in Figure 2, the IC50 values in all 5 species were within 3-fold (illustrated by the dashed lines) of this predicted relationship (solid line).

Establishment of this inter-species PK/PD scaling approach has allowed for its application in a variety of other Merck efforts that target Aβ production and CNS clearance. This method has subsequently informed Go / No-Go decisions on several compounds in early development.

Figure 2. Predicted Relationship Between IC50 and Free Fraction



Conclusions: 1) Semi-mechanistic PK/PD modeling allowed for characterization of the drug effect on CNS Aβ response across a variety of species including humans; 2) Because the same core equation describing response in brain tissue was used in all models, a cross-species scaling approach for the key IC50 parameter could be developed despite substantial differences in the time-course of response across the species; 3) Correction for plasma protein binding was required for successful inter-species scaling of IC50; and 4) Establishment of this scaling approach has allowed for its application in programs targeting Aβ to aid Go/No-Go decisions with regards to candidates in very early development and discovery

References:

[1] L.B. Rosen, J.A. Stone, et al. The Gamma Secretase Inhibitor MK-0752 Acutely and Significantly Reduces CSF Aβ40 Concentrations in Humans. Oral presentation at 10th International Conference on Alzheimer's Disease and Related Disorders (July 16-20, 2006, Madrid, Spain).