GastroPlus PBPK/PD Model Applied to Estimating Dose for an Elderly Population in an Alzheimer's Disease Clinical Trial

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Abstract

Objectives:

Certain neurosteroid metabolites of progesterone are known to be positive allosteric modulators of the GABAa receptor and have application as anticonvulsant, anxiolytic, and sedative hypnotic agents [1]. More recently 3α-hydroxy-5α-pregnan-20-one (AP-α) has been shown to promote neurogenesis in mice *in vitro* and *in vivo* [2-3]. In addition, AP-α has been shown to restore hippocampal-dependent learning and memory and neural progenitor cell survival in aging 3xTgAD and non-Tg mice [4]. Our objective was to explore the application of mechanistic absorption PBPK/PD modeling and simulation to the translation of basic science discoveries and preclinical data in support of developmental human clinical trials.

Methods:

ADMET Predictor(TM) (Simulations Plus, Inc.) was used to estimate the biopharmaceutical properties of AP-α [5]. Data from the literature on the pharmacokinetics and pharmacodynamics of AP-α in mice and humans were compared to PBPK/PD models built using GastroPlus 8.0™ (Simulations Plus, Inc.) to establish a prediction for a dosing regimen and expected human exposure in support of a developmental clinical trial in Alzheimer's patients. An indirect-link effect compartment PD model [6] was parameterized using data from *iv* administration of AP-α to healthy women, and measurements of the % change in saccadic eye velocity [7].

Results:

The mouse PBPK model was able to explain the observed plasma concentrations at three doses (1, 10, and 20 mg/Kg) and the observed cortex level following the 1 mg/Kg dose. Human clinical trial data for intravenous doses of AP-α linked to a pharmacodynamic model of saccadic eye movement were successfully modeled. Finally, an intravenous dosing regimen for an elderly population was proposed to achieve similar brain concentrations as observed in the mouse preclinical studies but to avoid the sedation inducing concentrations observed in the previous human clinical trials.

Conclusions:

The validated PBPK/PD model for allopregnanolone supplied prospective plasma and brain concentrations for *iv* dosing in an elderly population. Final results from the developmental clinical trial will be compared to this prediction when the studies are complete. GastroPlus can be used for translational research and facilitates multidisciplinary collaborations.

Biopharmaceutical and Clinical Data

ADMET Predictor™ (AP ver. 6.0, Simulations Plus, Inc.) was used to estimate the biopharmaceutical properties of APα (Table 1) [5]. The *in vitro* K_m and V_{max} for 3α-hydroxysteroid dehydrogenase (HSD) was from [8].

Table 1. APα *in silico* Estimates and Exper. Properties

Biopharmaceutical Property	Value	Source / Reference
S+logP	4.19	AP (ver. 6.0)
S+Sw	9.4 μg/mL	AP (ver. 6.0)
S+Rbp	0.73	AP (ver. 6.0)
HSD K_m	0.24 μM	[8]
HSD V_{max}	14.7 nmol/min/mg prot.	[8]

Where:
S+logP = Octanol/H2O log partition coefficient
S+Sw = Aqueous solubility at pH 7.0
S+Rbp = Blood to plasma concentration ratio

Methods

The physiologically-based pharmacokinetics (PBPK) and pharmacodynamics (PD) of APα was simulated using GastroPlus™ 8.0 (Simulations Plus, Inc., Lancaster, CA) and it's PBPKPlus™ module to estimate the tissue distribution, liver, kidney, and reproductive organ systemic clearance. Human physiologies were generated by the program's internal Population Estimates for Age-Related (PEAR) Physiology™ module [5][9][10]. Tissue/plasma partition coefficients were calculated using Berezhkovskiy's algorithm based on tissue composition and *in silico* physicochemical properties (Table 1) [11]. Metabolic clearance of APα in tissues was based on enzyme kinetic constants for APα from *in vitro* literature studies [8]. The PBPK model utilized fitted values for the expression levels of 3α-hydroxysteroid dehydrogenase however the relative amounts in liver, kidney, and reproductive organs was from *in vitro* data [12]. An indirect-link effect compartment PD model [6] was parameterized using the GastroPlus PDPlus™ module, plasma concentration vs. time data from intravenous administration of APα to healthy women, and measurements of the change in saccadic eye movement as a function of time [7].

Results:

Figures 1 and 2 illustrate that the PBPK/PD models correctly described the Cp-time profile and PD response of APα after a 3-step *i.v.* administration.

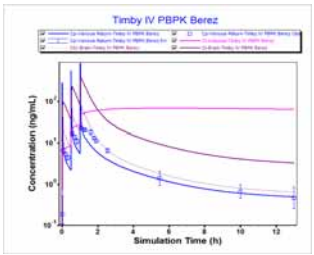

Figure 1 shows the observed plasma concentration vs. time data from a 3-step intravenous administration of APα at doses of 0.86 mg (time zero), 1.7 mg (30 min.), and 2.6 mg (1 hr.) [7]. The solid brown line is the predicted total brain concentration and the dotted brown line is the predicted unbound brain concentration. The magenta line is the predicted adipose tissue concentration.

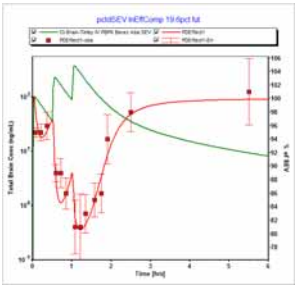

Figure 2 shows the observed % decrease in saccadic eye velocity (% of SEV on the right axis) and the simulated total brain concentration in green (left axis). Normal SEV = 350 – 600 deg/s [7].

.*Pharmacodynamic Model:*

Equations 1 and 2 were used to link the total brain concentration to the PD effect on % of SEV.

$$\frac{dC_e}{dt} = k_e(C_p - C_e) \qquad \text{Eqn. 1}$$

$$E = E_0 + \frac{E_{max}(C_e \times f_u)^{Hill}}{EC_{50}^{Hill} + (C_e \times f_u)^{Hill}} \qquad \text{Eqn. 2}$$

Where:

dC_e = change in effect compartment concentration
k_e = rate constant for transfer of APα from total brain to the effect compartment.
C_p = total brain concentration at each time step.
C_e = effect compartment concentration at each time step.
E = relative saccadic eye velocity
E_0 = initial saccadic eye velocity
E_{max} = maximal % decrease in saccadic eye velocity
EC_{50} = effect compartment total concentration for half maximal change in saccadic eye velocity.
Hill = Hill slope for the sigmoidal dose response relationship in the effect compartment
fu = fraction unbound in the effect compartment

The final parameter estimates for the pharmacodynamic model are presented in Table 2.

Table 2. PD Model Parameter Estimates

Parameter	Value (units) +/- Std. Dev
E_0	100 (% of normal deg/s) fixed value
E_{max}	-22.4 (%) ± 0.048
EC_{50}	22.4 (ng/mL) ± 0.002 (equiv. 70 nM)
Hill	2.08 ± 0.09
Fu	19.6% fixed value
k_e	8.83 (h^{-1}) ± 0.48

The validated PBPK/PD models were used to predict the plasma and brain concentrations of APα in the proposed study population of Californian males and females aged 60 to 80 years old using a range of intravenous injections from low doses (0.5 mg) with no predicted PD response to a dose (6 mg) with some slight sedation.

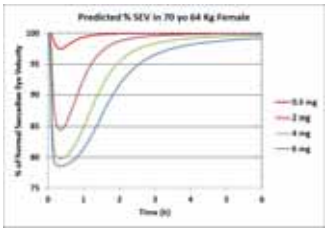

Figure 3 shows the simulated % of normal SEV profiles for a 70 year old female (64 Kg) following 0.5, 2.0, 4.0, and 6.0 mg doses.

Conclusions:

The validated PBPK/PD model for allopregnanolone supplied prospective plasma and brain concentrations for iv dosing in an elderly population. Final results from the developmental clinical trial will be compared to this prediction when the studies are complete. GastroPlus can be used for translational research and facilitates multidisciplinary collaborations.

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