Optimization of Fatigue Management: Utility of Physiologically Based Pharmacokinetic Modeling of a Stimulant

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Abstract

INTRODUCTION:
Fatigue is a pervasive factor in long-duration flight missions and can have critical consequences in terms of loss of lives, specialized equipment, and airframes. Stimulants are a common means to promote wakefulness. **Physiologically based models that can accurately recapitulate the impact of these stimulants on cognition have the potential to inform the timing and dosage of these stimulants for sustained operations, contributing to mission success. The utility of a physiologically based pharmacokinetic (PBPK) model of d-amphetamine (synonyms: d-amph, Dexedrine) for evaluating dosing scenarios was assessed.**

METHODS:
Using pharmacokinetic models of anti-fatigue agents together with a cognitive model (i.e., physiocognitive modeling) provides a framework to evaluate potential cognitive effects under different dosing scenarios. **We implemented, reproduced, and extended a previously published model of d-amphetamine dosimetry**. The model was tested to evaluate its ability to accurately reproduce published independent experimental data for scenarios not evaluated during model development. The model was also used to better understand the timing of d-amphetamine peak levels in the brain after dosing, since experimental measurements are not available.

RESULTS:
Previous simulations of d-amphetamine venous arm plasma levels after ingestion of immediate release formulations were within ~10% of the averaged experimental data used to calibrate the model. Model agreement with independent data sets was also excellent (all studies within 20%, on average). The time of the peak modeled concentration (Tmax) in venous arm blood was slightly earlier than the Tmax observed in experiments (3.0 vs. 3.5 hours after dosing). **The model simulations predict that brain concentrations of d-amphetamine peak 2.1 hours after dose administration, 0.9 hours earlier than the predicted timing of the peak concentration in venous arm blood.**

CONCLUSIONS:
The model was found to be accurate at predicting d-amphetamine concentrations in plasma, supporting the use of the model for simulating concentrations at the site of action (the brain). The timing of the highest levels of d-amphetamine in the brain is of particular interest as this information will be used as inputs into cognitive models**. Use of the model in coordination with a cognitive effects model is expected to support the optimization of timing and refinement of dosage for pharmacologic counter-fatigue interventions in the military.**

Background and Methods

BACKGROUND: CAPABILITY GOAL
- Generate knowledge to **inform dose amounts and timing of pharmacologic interventions to sustain cognitive performance** during extended-duration operations.

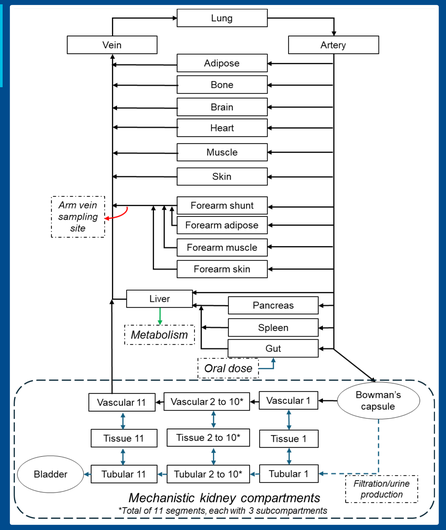
METHODS:
- Implement, verify, and validate published models, if available
  - Develop, refine, and validate new models, if necessary
- Simulate agent exposure scenarios to generate physiologically based estimates of blood, plasma, and/or brain concentration profiles to serve as inputs into cognitive impairment models
- Develop dosing recommendations for various scenarios (future work)

Results

Pharmacokinetic Model Selection

An existing deterministic model (fixed inputs, e.g., for an average individual) simulating the disposition of a single d-amphetamine dose (immediate- release formulation) in men and women, Huang et al. (2020), was identified (**Figure 1**). A key feature of interest was the mechanistic kidney submodel for simulation of scenarios with acidic urine (e.g., dehydration).

Figure 1. Structure of the model of d-amphetamine disposition (adapted from Huang et al. (2020)



Solid black lines indicate blood flow, bi-directional blue lines indicate diffusion

Pharmacokinetic Model Reconstruction

- We generated model equations based on information in the text and supplementary materials of Huang et al. (2020) and Huang and Isoherranen (2018 and 2020). The model was implemented in the open-source program Magnolia (version 1.3.9 beta).

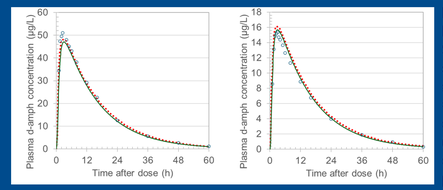
Pharmacokinetic Model Verification and Validation

- Verification: The model was verified by comparing original, published simulations in Huang et al. (2020) to new simulations generated using Magnolia (Figure 2 and 3).
- Validation: Model simulations were compared to measured concentrations in plasma. Data sources are described/cited in Tables 1 and 2.

Table 1. Summary of resources for model verification and validation

Data category	Comments
Model verification resources	Figures 2 and 3 (solid lines vs. dashed lines)
Model validation resources	
Data in Huang et al. (2020)	Figures 2 and 3 (solid lines vs. data)
Additional data from reports cited by Huang et al. (2020)	Data included extended-release formulation (4 conditions) and divided dosing of an immediate release formulation (1 scenario) (not shown)
Publications identified via PubMed	Clausen et al. (2005), Dolder et al. (2017), Roberts et al. (2015) (not shown)

Figure 2. Verification of human plasma time course simulations of Huang et al. (2020) and validation via corresponding group average measurements originally reported in CDER (2002).



Left: 14.1 mg d-amphetamine base
Right: 4.7 mg d-amphetamine base
Symbols: open circles = measured data from CDER (2002) (group average, n = 18 subjects); filled circles = predicted venous arm plasma concentration of Huang et al. (2020) (digitized). **Lines:** predicted concentrations in venous arm plasma per reconstructed model

Figure 3. Verification of human plasma time course simulations of Huang et al. (2020) and validation via measurements originally reported in Beckett et al. (1969) for baseline (uncontrolled), acidic, and basic (alkaline) urine conditions; dose: 11 mg d-amphetamine base

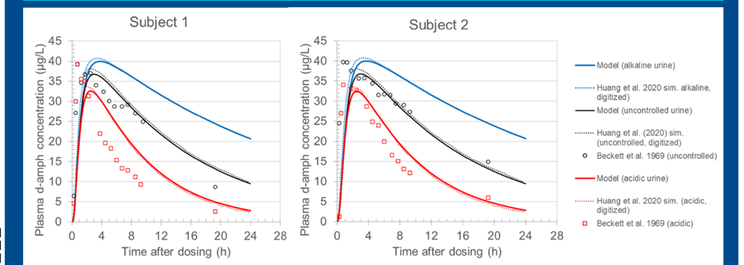
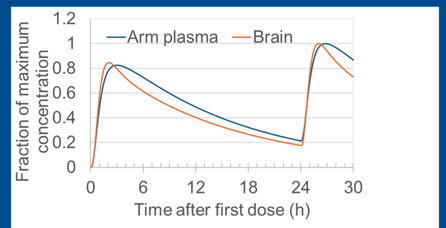


Table 2. Summary of model evaluation of predicted vs. measured group average or median arm plasma concentrations by study design features

Studies	Metric		
	Bias (Simulation/measured) [a]	Average absolute fold error [a]	Maximum absolute fold error across all measurements
All studies with group data (n = 13)	0.979 (0.867-1.16)	1.13 (1.05-1.20)	2.02
IR formulation, fasted volunteers (n = 3)	1.04 (0.926-1.16)	1.10 (1.05-1.16)	1.45
XR formulation, fasted volunteers (n = 4)	0.926 (0.867-0.980)	1.13 (1.06-1.19)	1.33
Daily dosing (7 days) (n = 2)	0.920, 1.16	1.13, 1.16	1.30, 1.45
Fed volunteers (n = 2)	0.96, 1.04	1.20, 1.20	2.02

[a] Geometric mean (range); 1 = perfect agreement between predicted and measured values

Figure 4. Predicted brain vs. arm plasma time course for d-amphetamine



The predicted peak concentrations of d-amphetamine in the target tissue (brain) occurs earlier (2.1 hours after dosing) than the peak concentration in venous arm plasma (3.0 hours after dosing)

Discussion

- Accuracy of our implementation of the Huang et al. (2020) d-amphetamine model was excellent.
  - Simulations of the recreated model were typically within ~5% of values in the original publication.
  - Discrepancies were small and either less than or similar to the discrepancies between the model predictions and the validation/calibration data used by Huang et al. (2020).
  - Model verification and validation were deemed successful.
- We compared the model predictions to a wider variety of data (Table 2) than were initially used for its calibration and initial validation by Huang et al. (2020). Our findings support the use of the model for scenarios with repeated and extended-release formulations and fed (rather than fasted) volunteers.
- We have started to explore implications of the model simulations with respect to fatigue management.
  - With once-per-day dosing, peak concentrations in the target tissue (brain) are predicted to occur ~1 hour earlier than peak concentrations at the sampling site (venous arm blood).
  - While blood concentrations are important for evaluating pharmacokinetic features such as interindividual variability, the ability to estimate levels at the target site is expected to improve fidelity of the pharmacodynamic (effects) modeling.

Conclusions/Next Steps

- The model was found to be accurate at predicting d-amphetamine concentrations in plasma, supporting the use of the model for simulating concentrations at the site of action (the brain). The timing of the highest levels of d-amphetamine in the brain is of particular interest as this information will be used as inputs into cognitive models.
- Next steps include sensitivity analysis, population modeling incorporating key determinants of variability, and integration with cognitive effects modeling efforts
- Use of the model in coordination with a cognitive effects model is expected to support the optimization of timing and the refinement of dosage for pharmacologic counter-fatigue interventions in the military.

References

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Disclaimer & Acknowledgements

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