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In Silico Predictive Modeling of the Pharmacokinetic (PK) Profiles of Nasal Sprays in Adults and Children

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PURPOSE

For locally-acting nasal drug products like suspension-based nasal sprays, a complex array of characteristics affect the in vivo performance.

These characteristics can include the formulation, device, nasal anatomy, and the region of the depositing particles within the nose. To facilitate a better understanding of how these characteristics may impact in vivo performance metrics like systemic exposure, a pharmacokinetic (PK) model was developed for predicting the exposure of triamcinolone acetonide (TAA) in adult and pediatric patients following nasal spray administration.

OBJECTIVE

Develop a computational fluid dynamics (CFD) model coupled with a dissolution, absorption, and clearance (DAC) methodology can be used to predict the PK profiles (CFD-DAC-PK) for nasally-administered TAA (110, 220, and 440 mcg) in the adult and pediatric models [1, 2].

METHODS

A set of adult and pediatric in vitro 3D nasal cavity geometries (low (L), medium (M), and high (H) drug delivery models) [3] were used as CFD models in ANSYS FLUENT 2022 R2 and unwrapped into 2D 'planar' models to represent the airway surface liquid (ASL) and epithelium regions using MATLAB R2022a and the CFD-DAC-PK approach (Figure 1).

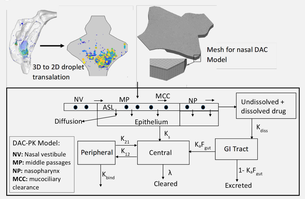
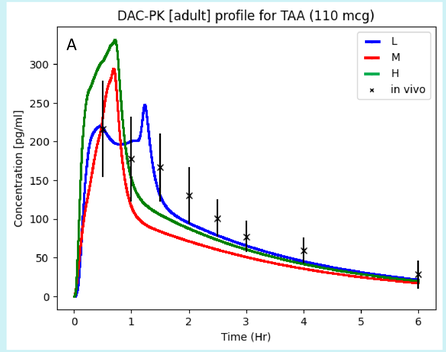


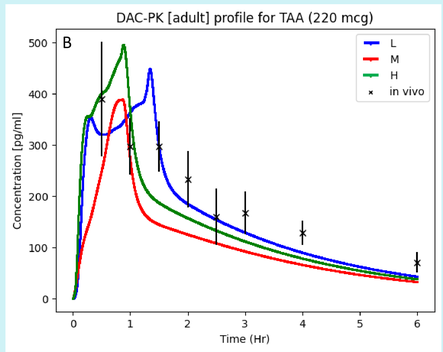
Figure 1: Translation of the 3D model to a 2D 'planar' mesh (top) used in the coupled CFD-DAC-PK approach (bottom) [1].

The DAC mechanistic models of suspended TAA particles included simulations of dissolution (D), drug diffusion from the ASL to the epithelium, and posterior epithelium absorption (A) along with mucociliary clearance (C). This model was combined with a compartmental PK model to evaluate systemic exposure. The model was initialized by specifying mucus and tissue properties in the ASL and epithelium regions. Laminar fluid flow equations were solved in the DAC-PK model by implementing a user defined function for specifying liquid mass source in the ciliated region (posterior nasal cavity) [2]. Adult PK model parameters were estimated based on in vitro and/or in vivo data [3,4]. Allometric scaling was done for the pediatric models where the predicted PK profile data were plotted alongside the in vivo data and analyzed in Python 3.10 for the area under the curve (AUC).

RESULTS

Results: Adult Model





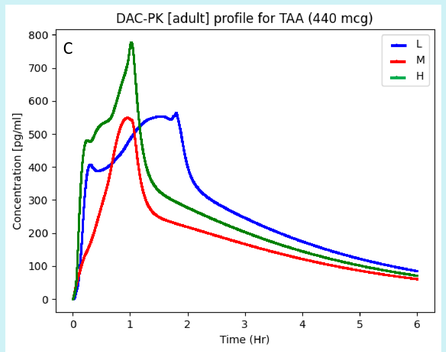
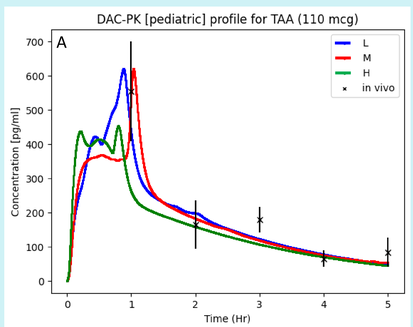


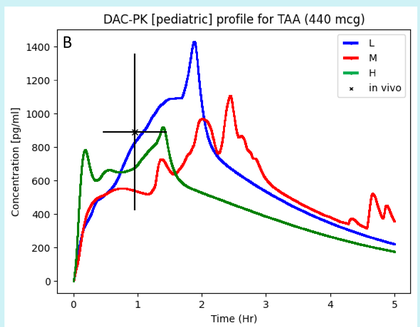
Figure 2: Adult DAC-PK profiles shown for **A)** 110 mcg, **B)** 220 mcg, **C)** 440 mcg doses of TAA, and **D)** summary of the PK outcomes, T_{max}, C_{max}, and AUC. For the DAC-PK profiles, a single run is shown. The in vivo data shown are mean with standard deviation of the plasma concentrations at each time point from all the subjects evaluated (n = 15) [4].

Figures 2A and 2B show the plasma concentration profiles for the three adult models (L/M/H) for a nasally administered TAA dose of 110 mcg and 220 mcg, respectively, compared to publicly available *in vivo* data [4]. The DAC-PK model appeared to overestimate the maximum plasma concentration (C_{max}) for all three adult models compared to the in vivo data at the 110 mcg and 220 mcg TAA dose, with the exception of the M model at the 220 mcg TAA dose. However, the predicted AUC values appeared to agree with the in vivo data for the adult L and H models for both the 110 mcg and 220 mcg TAA dose (Figure 2D). Figure 2B shows that the predicted C_{max} values for the adult M model was comparable with the in vivo values at the 220 mcg TAA dose, and the predicted AUC for the L and H model appeared to agree with the in vivo data.

D	*Adult*	Tmax (Hr)	Cmax (pg/ml)	AUC
110 mcg	**L**	1.23	247.53	523.74
	M	0.69	294.45	414.28
	H	0.71	331.9	535.92
	in vivo	0.5	215.95	517.33
220 mcg	**L**	1.34	448.86	978.46
	M	0.86	388.66	674.34
	H	0.88	495.44	905.54
	in vivo	0.5	389.72	979.34
440 mcg	**L**	1.8	563.91	1635.3
	M	0.95	549.99	1102.93
	H	1.01	777.84	1508.62

Results: Pediatric Model





C	*Pediatric*	Tmax (Hr)	Cmax (pg/ml)	AUC
110 mcg	**L**	0.88	621.13	952.45
	M	1.03	621.06	907.86
	H	0.8	453.11	835.3
	in vivo	1	554.05	727.03
440 mcg	**L**	1.88	1429.71	2997.38
	M	2.44	1106.89	2843.68
	H	1.39	917.99	2308.54
	in vivo	0.96	888.2	3071.5

Figure 3: Pediatric DAC-PK profiles shown for **A)** 110 mcg, **B)** 440 mcg doses of TAA, and **C)** summary of the PK outcomes, T_{max}, C_{max}, and AUC. For the DAC-PK profiles, a single run is shown . The in vivo data for the 110 mcg dose shown is a mean with the standard deviation of the plasma concentrations at each time point from all the subjects evaluated (n = 15) [4]. For the 440 mcg dose, the in vivo data are mean with the standard error of the T_{max} and C_{max} from all the subjects evaluated (n = 25-28) [5].

RESULTS (CONT.)

Figures 3A and 3B show the plasma concentration profiles for the three pediatric models (L/M/H) for a nasally-administered TAA dose of 110 and 440 mcg, respectively. The DAC-PK model appeared to overpredict C_{max} with a comparable T_{max} for the pediatric M model; however, it underpredicted the T_{max} for the pediatric L and H models, while overpredicting the AUC compared to the in vivo data at the 110 mcg dose (Figure 3C). The DAC-PK model appeared to predict a C_{max} value that is comparable to the in vivo data for the pediatric H model and a comparable value of AUC to that presented in the in vivo study by Nayak, et al. [5] for the pediatric L model at the 440 mcg TAA dose (Figure 3B and 3C). However, numerical instability was observed for the pediatric M model for the 440 mcg TAA dose, which remains to be resolved.

CONCLUSIONS

Overall, the DAC-PK modeling approach appeared to predict comparable plasma concentration profiles in a model-specific manner. The adult L and H model PK profile predictions showed comparable AUC values to in vivo measurements for the 110 and 220 TAA mcg doses, while the adult M model appeared to underestimate the AUC. Interestingly, the C_{max} in the adult M model was comparable for the 220 mcg TAA dose, with a higher T_{max} but a lower AUC compared to the in vivo outcomes, suggesting a faster clearance mechanism. However, both the C_{max} and AUC were overestimated for the 110 mcg TAA dose in the pediatric L and M model while only the AUC was overestimated for the H model, which suggested a slower clearance mechanism. Spray wall interactions, among other factors, will be considered in future models to improve predictability of the developed models.

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