A Hybrid CFD-PBPK Approach to Simulate Deposition, Absorption, and Bioavailability of Corticosteroid Nasal Sprays

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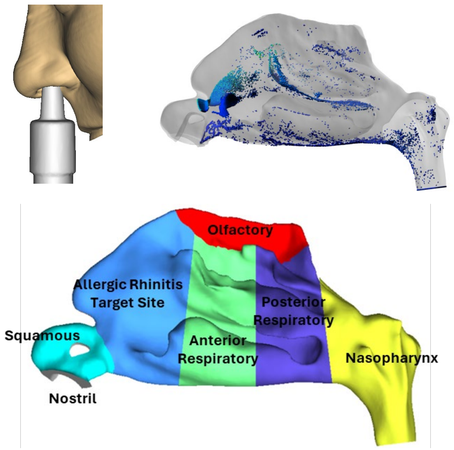
Introduction

- Aqueous suspension corticosteroid nasal sprays are commonly used to treat rhinitis.
- Nasal spray deposition depends on the droplet size and spray and use parameters such as cone angle, spray speed, and nozzle position.
- Absorption depends on regional nasal deposition patterns and the physicochemical properties of the active pharmaceutical ingredient (API).
- Computational fluid dynamics (CFD) models were developed to predict nasal spray droplet deposition.
- Physiologically based pharmacokinetic (PBPK) models were developed to simulate corticosteroid absorption and bioavailability.
- The hybrid CFD-PBPK approach used regional deposition estimates from CFD models to inform mass inputs to the PBPK model to study effects of nasal spray deposition patterns on corticosteroid bioavailability.

Approach

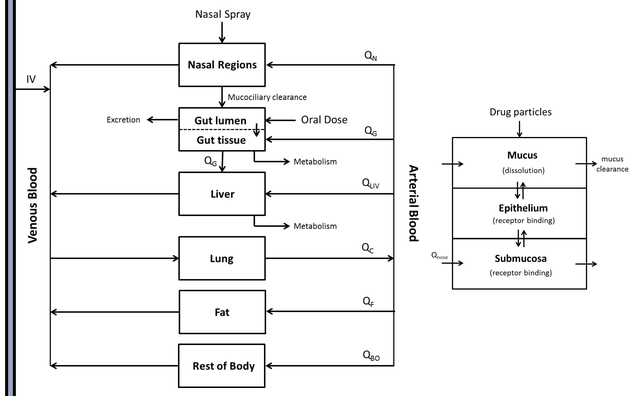
- CFD simulations were used to estimate regional droplet deposition from nasal sprays in healthy and rhinitic subjects [1].
- The nasal cavity models were subdivided into 6 anatomical regions (Fig. 1).
- A PBPK model was developed (MATLAB, R2024a) to simulate absorption and bioavailability of aqueous suspension corticosteroid nasal sprays (Fig. 2).
- Key elements of the PBPK model include nasal spray deposition estimates, dissolution, diffusion through nasal epithelium, mucociliary clearance, absorption in the gastrointestinal tract, glucocorticoid receptor binding, plasma protein binding, and metabolism.
- CFD-PBPK model simulations were conducted for nasal spray administration of fluticasone propionate (FP), mometasone furoate (MF), and budesonide (Bd) (Figs. 3-5).

Figure 1: Healthy and rhinitic nasal CFD models were used to simulate corticosteroid nasal spray deposition (rhinitic model shown here).



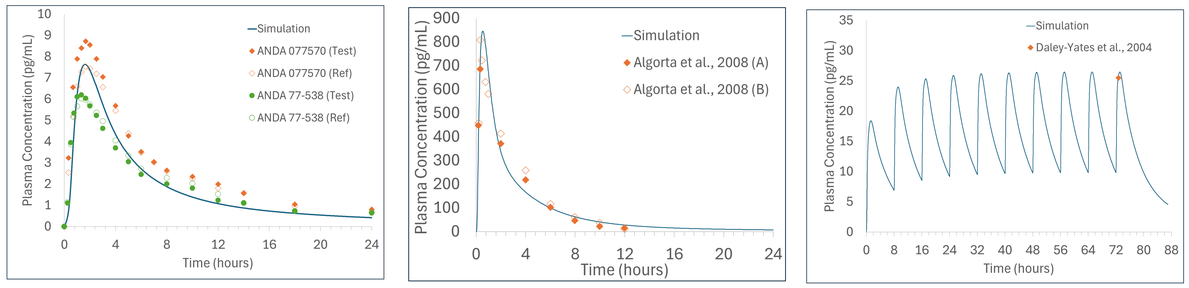
The majority (> 90%) of predicted nasal spray deposition occurred in the Squamous and Allergic Rhinitis Target Site regions.

Figure 2: The whole-body PBPK model included key kinetic processes to simulate absorption and bioavailability of nasal sprays (left), including a detailed multi-layer description of the nasal mucosa in each anatomical region (right).



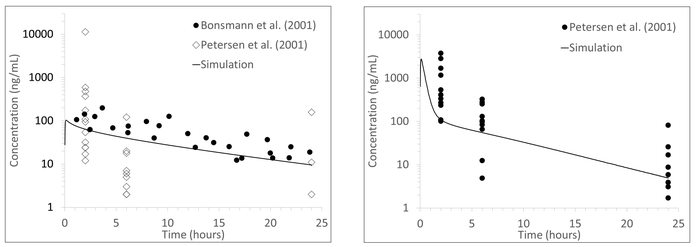
Multiple exposure routes (IV, oral, nasal spray) were included in the PBPK model to take advantage of the numerous experimental studies with FP, MF, and Bd.

Figure 3: PBPK model predictions of plasma concentrations of FP (left), Bd (middle), and MF (right) following nasal spray administration compared with in vivo pharmacokinetic data.



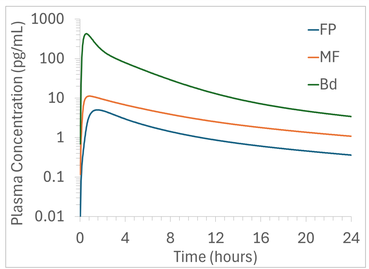
200 µg FP nasal spray | **512 µg Bd nasal spray** | **10 800 µg MF nasal sprays**

Figure 4: PBPK model predictions of nasal epithelial concentrations of FP (left) and Bd (right) following nasal spray administration compared with in vivo pharmacokinetic data.



100 µg FP nasal spray | **128 µg Bd nasal spray**

Figure 5: PBPK model predictions of FP, MF, and Bd plasma concentrations following a 100 µg nasal spray dose.



Conclusions

- PBPK model predictions compared well with experimental data for nasal tissue and plasma concentrations.
- Despite similar predicted regional nasal deposition, there were large differences in nasal epithelial and plasma concentrations between steroids.
- Pharmacokinetic differences, such as the large differences in maximum plasma concentration (C_{max}) for nasal tissue and plasma concentrations, are primarily due to differences in physico-chemical properties (e.g., solubility) between steroids.
- The CFD-PBPK approach can be used to examine pharmacokinetic differences between steroids and assess effects of regional nasal deposition on local nasal tissue and systemic kinetics.

References

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Acknowledgments

Funding was provided by contract 75F40119C10079 from the Department of Health and Human Services (DHHS), U.S. Food and Drug Administration. Views expressed here do not reflect the official policies of the DHHS; nor does mention of trade names, commercial practices or organizations imply endorsement by the U.S. Government.