A Physiologically-Based Pharmacokinetic Model to Estimate Absorption and Bioavailability of Corticosteroid Nasal Sprays

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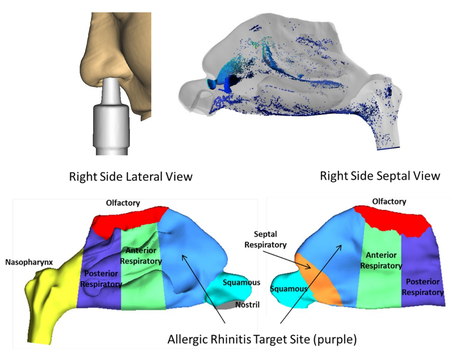
Introduction

- 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 and physiologically-based pharmacokinetic (PBPK) models can be used to describe deposition, absorption, and bioavailability of intranasal corticosteroid sprays.

Approach

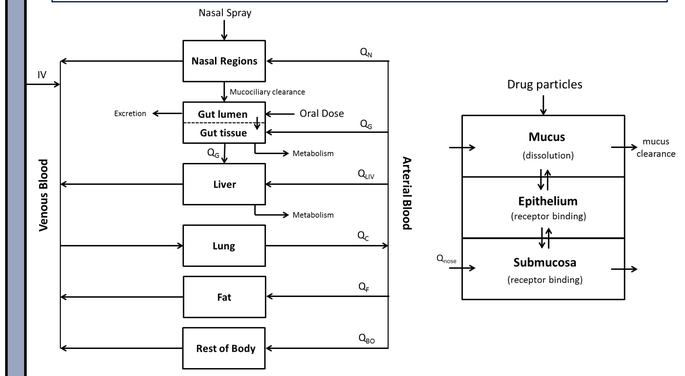
- CFD simulations were used to estimate regional droplet deposition from nasal sprays in healthy and rhinitic subjects [1].
- The nasal cavity models were subdivided into 7 anatomical regions (Fig. 1).
- A PBPK model was developed using MATLAB R2020a (The Mathworks, Inc., Natick, MA, USA) to simulate 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.
- PBPK model simulations were conducted for fluticasone propionate (FP) and budesonide (Bd) nasal sprays using a uniform API particle size of 3 µm and were run to simulate 24 hours of exposure following nasal spray administration (Figs. 3, 4).

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



Average (healthy, rhinitic, left and right side) deposition fractions for FP and Bd were 55% and 51% in the squamous region, 15% and 14% in the septal respiratory region, and 27% each in the allergic rhinitis target site region, respectively. Deposition in all other regions was < 2%.

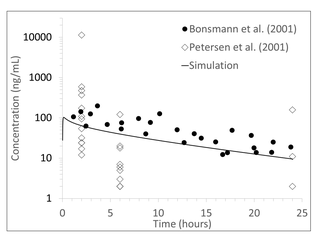
Figure 2: The whole-body PBPK model included key kinetic processes to simulate absorption and bioavailability of nasal sprays (left), including a detailed multi-layer description of the nasal mucosa in each anatomical region (right).



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

Nasal epithelial concentrations

100 µg FP nasal spray



128 µg Bd nasal spray

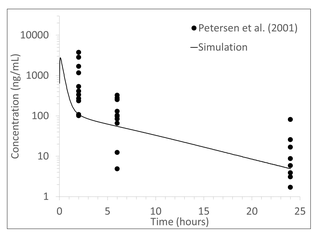
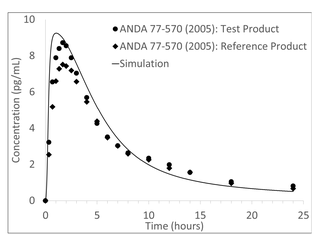


Figure 3: PBPK model predictions of nasal epithelial concentrations of FP (left) and Bd (right) following nasal spray administration compared with in vivo pharmacokinetic data.

Plasma concentrations

200 µg FP nasal spray



512 µg Bd nasal spray

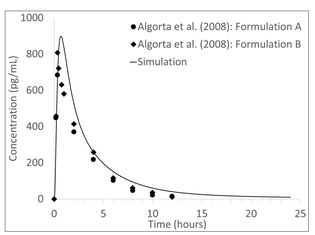


Figure 4: PBPK model predictions of plasma concentrations of FP (left) and Bd (right) following nasal spray administration compared with in vivo pharmacokinetic data.

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 FP and Bd.
- Pharmacokinetic differences, such as the large differences in C_{max} for nasal tissue and plasma concentrations, are primarily due to differences in solubility (0.14 µg/mL for FP, 16 µg/mL for Bd).
- Future work:
  - Study nasal deposition in additional healthy adults, rhinitic adults, and healthy children.
  - Additional steroids with a range of solubilities and other physicochemical properties.

References

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