A CFD-PBPK Model to Simulate Nasal Absorption and Systemic Bioavailability of Intranasal Fluticasone Propionate

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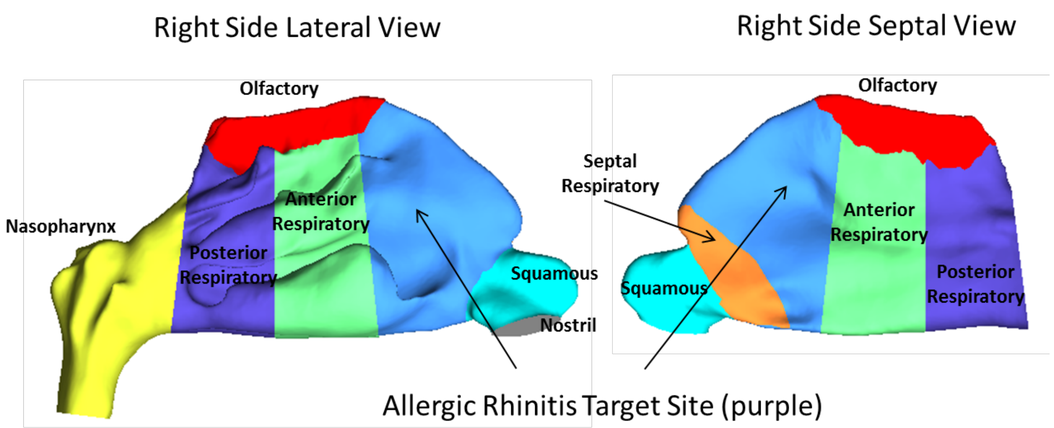
INTRODUCTION

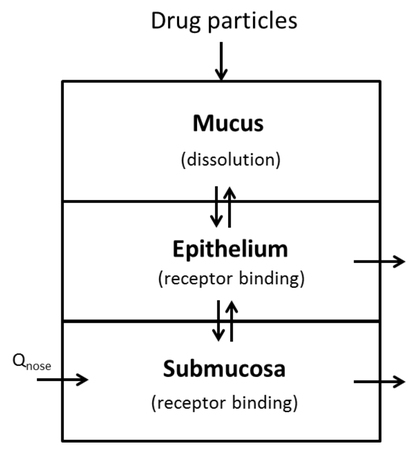
- Fluticasone propionate (FP) suspension nasal sprays are commonly prescribed to treat symptoms associated with rhinitis.
- FP nasal spray has been reported to have high activity in the nose and low systemic bioavailability [1].
- The efficacy of suspension nasal sprays depends on their droplet deposition patterns in the nose and the subsequent absorption of the drug through the nasal mucosa.
- Computational fluid dynamics (CFD) simulations can be used to simulate droplet transport and deposition from nasal sprays [2].
- Physiologically-based pharmacokinetic (PBPK) models need to be developed to provide quantitative measures of the absorption and distribution of nasally administered drugs throughout the body.



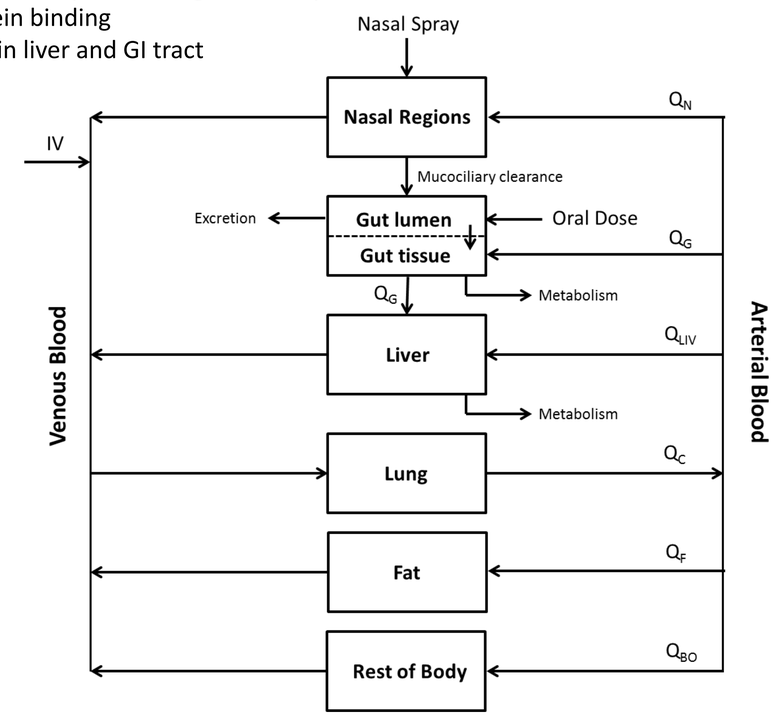
A nasal CFD model was divided into anatomical regions for nasal spray droplet deposition analysis (see Kimbell et al. poster)

METHODS

- CFD simulations were used to estimate droplet deposition of Flonase™ nasal spray in anatomical regions
- A PBPK model was developed to simulate absorption and distribution of FP
- Model features:
  - Well-mixed compartments for nasal regions, gut, liver, lung, fat, and rest of body
  - Drug administration routes: nasal, iv, oral
  - CFD simulation results used as inputs for FP nasal spray simulation
  - Drug particle dissolution in nasal mucus and gut
  - Diffusion through nasal epithelial layers
  - Mucociliary clearance
  - Glucocorticoid receptor binding in nasal epithelium
  - Plasma protein binding
  - Metabolism in liver and GI tract



Each nasal region was subdivided into epithelial layers in the PBPK Model

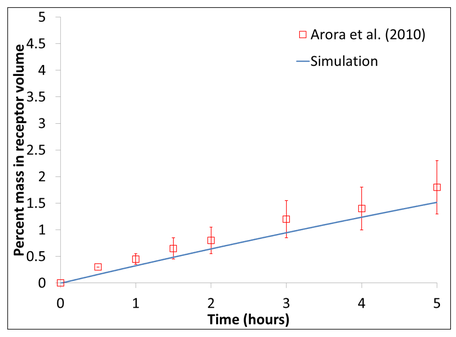


Overall PBPK Model Structure

RESULTS

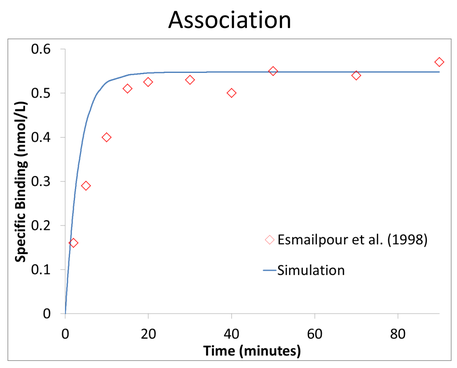
Dissolution:

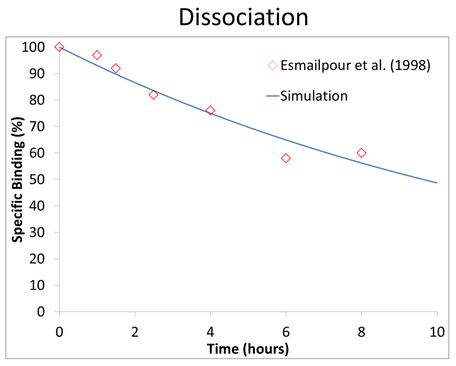
- Dissolution was governed by the Noyes-Whitney equation
- A submodel was developed to compare dissolution + diffusion with in vitro data from a Transwell™ system [3]



Receptor Binding:

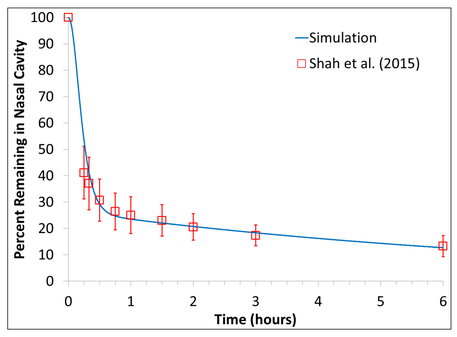
- Binding to the glucocorticoid receptor followed classic receptor:ligand kinetics
- Association and dissociation rate constants were derived from in vitro data [4]





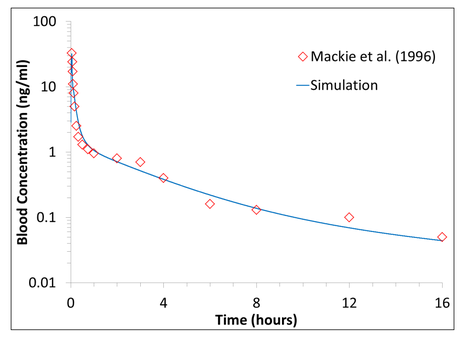
Mucociliary Clearance:

- Mucociliary clearance velocity = 8 mm/min
- PBPK simulation results of nasal clearance were compared to in vivo data [5]



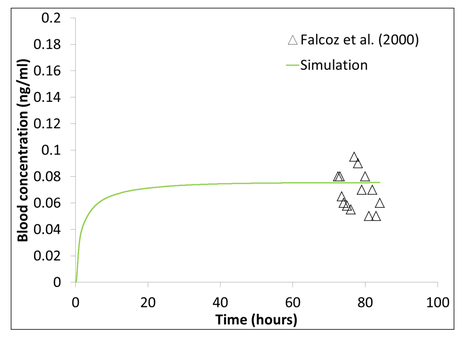
Metabolism:

- Metabolic parameters (V_{max}, K_M) were derived from in vitro studies [6]
- PBPK simulation: iv dose of 500 µg FP [7]



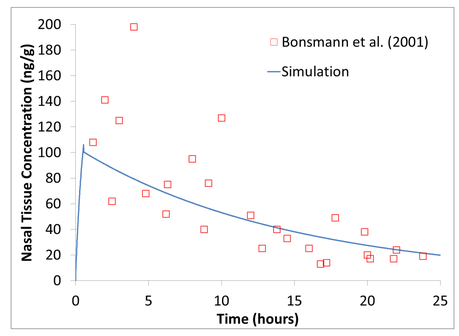
Oral Absorption:

- Transfer rate from gut lumen to gut tissue limits oral absorption of FP
- PBPK simulation: oral doses of 10 mg FP twice daily for four days [8]



Nasal Spray:

- PBPK simulation of FP nasal spray: 2 x 50 µg
- Regional deposition estimated from nasal CFD model
- Model simulation results compared with data from Bonsmann et al. (2001) [9]
- Drug retention in nasal epithelia primarily due to receptor binding
- Blood concentrations remained very low (< 50 pg/ml)



CONCLUSIONS

- Due to its low solubility, FP dissolution is very slow
- Rapid association to the glucocorticoid receptor and slow dissociation results in elevated nasal tissue concentrations for up to 24 hours
- Systemic bioavailability of FP following nasal spray is very low
- Future work will entail extension of the PBPK modeling approach to other corticosteroids

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