A Physiologically-Based Pharmacokinetic Model Framework to Estimate Systemic Bioavailability of Fluticasone Propionate Nasal Spray

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INTRODUCTION

• Fluticasone propionate (FP) is a topical steroid generally delivered as an aqueous suspension nasal spray to treat nasal symptoms associated with rhinitis.

• FP nasal spray has been reported to have high activity in the nose and low systemic bioavailability [1, 2].

• The pharmacokinetics of FP and other intranasal corticosteroids are important to assess for safety concerns.

• Pharmacokinetic models are useful tools that provide quantitative measures of the absorption and distribution of nasally administered drugs throughout the body.

• Absorption of nasal steroid sprays may depend on their regional deposition in the nose.

• In this study, a physiologically-based pharmacokinetic (PBPK) model framework was developed to estimate systemic bioavailability of FP given by iv injection and administered as a nasal spray.

APPROACH

• The PBPK model structure for nasal sprays contained compartments for the nasal regions, lung, liver, and arterial and venous blood. The remaining body tissues were lumped into a single compartment (Fig. 1).

• Blood flow rates and tissue volumes were taken from the literature [3]. Body compartments used a flow-limited structure.

• The nasal cavity was subdivided into seven anatomical regions to assess localized nasal spray deposition (Fig. 2).

• The nasal regions were included in the PBPK model and were further subdivided into three subcompartments representing the mucus, epithelium, and submucosal layers (Fig. 3).

• Nasal surface areas and FP nasal spray deposition fractions were obtained from computational fluid dynamics (CFD) simulations (see poster by Kimbell et al. [4])

• First-order rate constants governed the elimination of drug through the liver, active transport between nasal epithelial layers, and the elimination of drug from the nasal epithelium.

• The PBPK model was designed to accommodate two exposure routes: iv or nasal spray.

• PBPK model simulations were performed using AcslX (Aegis Technologies, Inc.).

CFD-PBPK MODEL DESCRIPTION

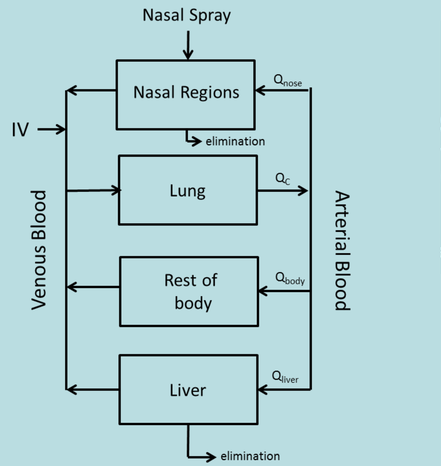

Figure 1: The PBPK model structure used to estimate systemic bioavailability of FP given by iv injection or nasal spray. Drug given by iv was input directly into the venous blood. Localized FP nasal spray deposition was estimated from a CFD model [4].

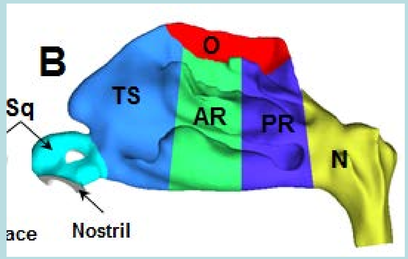

Figure 2: Nasal regions in a healthy adult nasal CFD model (from Kimbell et al. poster [4]).

SQ: Squamous
SR: Septal Respiratory
TS: Target Site
AR: Anterior Respiratory
PR: Posterior Respiratory
O: Olfactory
N: Nasopharynx

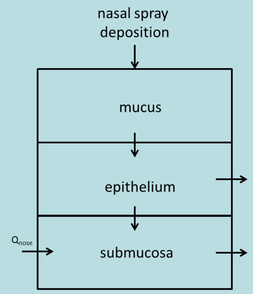

Figure 3: Nasal epithelial structure for each nasal region in the PBPK model.

RESULTS

IV Injection:

- In the study by Mackie et al. (1996), subjects were given an iv dose of 500 µg FP [1].
- This data was used to calibrate the elimination rate constant in the PBPK model (Fig. 4).

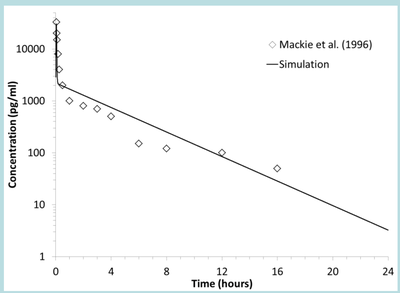

Figure 4: Plasma concentrations following iv exposure to 500 µg FP.

Nasal Spray:

- In the study by Daley-Yates et al. (2001), volunteers received four separate 800 µg doses of FP nasal spray separated by eight-hour intervals [2].
- The elimination and transfer rate constants in the nasal regions of the PBPK model were calibrated to the plasma data (Fig. 5).

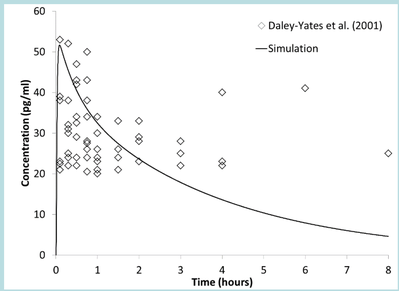

Figure 5: FP plasma concentrations following four 800 µg doses administered by nasal spray.

DISCUSSION

• The PBPK model simulations conducted in this study were designed to mimic the experimental scenarios for iv exposure [1] or nasal spray [2].

•The PBPK model structure was able to capture the clearance kinetics of FP in the systemic circulation following iv exposure (Fig. 4).

• The model accurately captured the decrease in FP systemic concentration following nasal spray exposure (Fig. 5). Under-predictions in the latter half of the time period could be due to the data being close to the limit of detection (20 pg/ml).

• The current PBPK model structure uses regional deposition estimates from CFD simulations of nasal sprays and is able to simulate systemic bioavailability of FP following intranasal or iv administration.

• Future work will involve the replacement of calibrated rate constants with more specific transfer and clearance mechanisms, including rates of dissolution, diffusion, and metabolism.

• The PBPK model will also be extended to other intranasal steroids to compare nasal tissue concentrations and systemic bioavailability as a function of solubility.

REFERENCES

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