Development of a Physiologically Based Pharmacokinetic (PBPK) Model for Predicting Deposition and Disposition following Inhaled and Intranasal Administration

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Introduction & Background

The selection of a biologically active molecule as a successful inhaled therapeutic agent depends on its pharmacokinetic and safety properties and concentration profile(s) in both the plasma and the pulmonary tissues. In recent decades, pharmacokinetic (PK) modeling, especially Physiologically Based Pharmacokinetic (PBPK) modeling (1), has become a powerful tool for predicting concentration-time profiles for drugs of interest (2, 3). Extension of the PBPK methodology from traditional dosage forms to intranasal/inhalation routes could provide useful information for the design and selection of drug candidates.

This work describes the extension of the modeling and simulation software GastroPlus™ (Simulations Plus, Inc.) (4), to include administration via inhaled and intranasal routes and its application to mechanistically model disposition following pulmonary administration of budesonide, a non-halogenated corticosteroid that is among the most effective inhaled medications available for patients with persistent asthma (5).

Methods

The model describes the lungs as a collection of up to 5 compartments: an optional nose (containing the anterior nasal passages), extra-thoracic (naso- and oro-pharynx and the larynx), thoracic (trachea and bronchi), bronchiolar (bronchioles and terminal bronchioles) and alveolar-interstitial (respiratory bronchioles, alveolar ducts and sacs and interstitial connective tissue). The scheme is similar to that adopted in the ICRP66 model (6) and is shown in Figure 1.

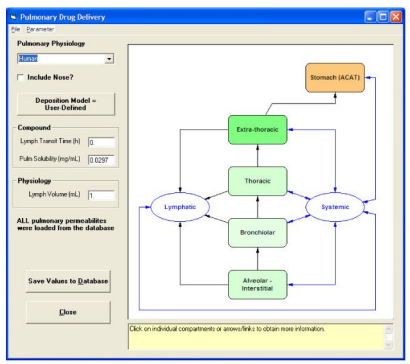

Figure 1. Pulmonary drug delivery interface within GastroPlus™.

The model allows partial exhalation immediately after administration, while the remainder is either swallowed or deposited in the mucus/surfactant layer lining the airways of the various pulmonary compartments. The relative quantities deposited in each pulmonary compartment can be predicted (based on the size and density of the inhaled particles) through a built-in deposition model as described in (6), or can be specified manually by the user. Both the built-in deposition model (as shown in Figure 2) and the deposition scheme described in the Multiple-Path Particle Dosimetry (MPPD) model (7) were used for the budesonide analysis.

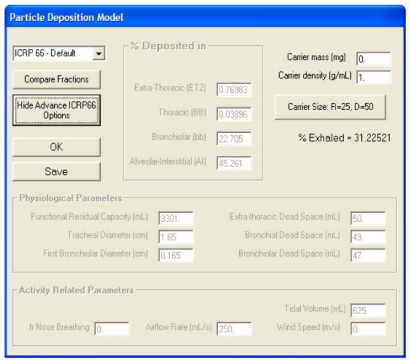

Figure 2. Built-in GastroPlus™ deposition model.

Upon deposition, the disposition of the drug is dictated by mucociliary transit, swallowing, dissolution, absorption into pulmonary cells and eventually into systemic circulation, accounting for metabolism, all while accounting for fractions unbound in the mucus/surfactant layers and the cells. The dissolution rate in the pulmonary mucus is described by a Noyes-Whitney equation (8), taking into account the solubility of the compound at the pH of the mucus (pH = 6.9) (9), particle size, particle density, and water diffusion coefficient. The passive absorption of drugs is driven by a concentration gradient with rates dependent on physiological (e.g., surface area) and drug-dependent physicochemical properties (e.g., permeability) for each compartment. The pulmonary model is connected to the advanced compartmental absorption and transit ACAT™ (10) gastrointestinal tract model and pharmacokinetic models in GastroPlus to simulate drug appearance in plasma after combined absorption from the airways and the gastrointestinal tract (to account for the often large swallowed portion of an inhaled dose), as well as drug uptake by the nasal-pulmonary tissues from the plasma after oral or systemic administration.

For the inhaled PK model, human lung physiological parameters (surface area, thickness and volume for the mucus and cell) for each compartment were obtained from the literature. The drug-dependent input parameters (including pulmonary permeability) were obtained from values reported in the literature. Systemic PK was described through a three-compartment model within GastroPlus, with parameters obtained from a PK study conducted within GlaxoSmithKline using the PKPlus™ Module within GastroPlus (Simulations Plus, Inc.) (4).

Results

Figure 3 shows the predicted plasma concentration-time profile and the measured values for budesonide obtained from a GlaxoSmithKline study of sixteen healthy volunteers. The simulation results closely match the observed values. No model parameters were fitted from the observed data. The accuracy of the pure prediction provides an initial validation of the model for budesonide.

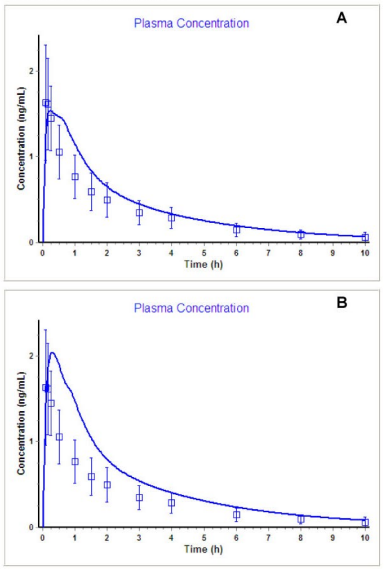

Figure 3. Predicted (line) versus observed (points from GSK Study No FMS10031) plasma concentration time profile for 400µg inhaled budesonide. Initial deposition fractions were calculated using (A) MPPD [7] and (B) ICRP 66 [6] models.

Conclusions

- The inhaled budesonide PBPK model provided a very reasonable agreement between observed and simulated plasma concentration-time data; with no calibration of the model (i.e., no input parameters were fitted).
- We believe this new capability will become a valuable tool for scientists in the development and understanding of new inhaled and intranasal drug candidates.
- Additional pulmonary compounds are being analyzed and there are plans to increase the sophistication of the model by incorporating additional mechanisms (e.g., pulmonary transporters) and functionality.

References

1. Nestorov, I. (2003), "Whole Body Pharmacokinetic Models", *Clin. Pharmacokinet.*, 42(10), pp 883-908.
2. Jones, H.M., Parrott, N., Jorga, K., Lave, T. (2006) "A novel strategy for physiologically based predictions of human pharmacokinetics", Clin Pharmacokinet, 45, pp 511-542.
3. De Buck, S.S., Sinha, V.K., Fenu, L.A., Nijsen, M.J., Mackie, C.E., Gilissen, R.A.H.J. (2007) "Prediction of human pharmacokinetics using physiologically based modeling: A retrospective analysis of 26 clinically tested drugs", Drug Metab Dispos, 35, pp 1766-1780.
4. www.simulations-plus.com (visited February 4, 2010)
5. "Global Strategy for Asthma Management and Prevention" (Revised 2002), National Institutes of Health; National Heart, Lung, and Blood Institute.
6. Smith, H. (ed) (1995), ICRP Publication 66: Human respiratory tract model for radiological protection, Elsevier Health Sciences.
7. http://www.ara.com/products/mppd.htm (visited February 4, 2010)
8. Shargel, L. and Yu, A. B. C. (1999). Biopharmaceutics and Pharmacokinetics, McGraw Hill, New York, 4th ed., pg 132.
9. Effros, R. M., Chinard, F.P. (1969), "The In Vivo pH of the Extravascular Space of the Lung", *J. Clin. Invest.*, 48, pp 1983-1996
10. Agoram, B., Woltosz, W.S., Bolger, M.B. (2001), "Predicting the impact of physiological and biochemical processes on oral drug bioavailability", *Adv. Drug Deliv. Rev.*, 50(suppl1), pp S41-S67.

Acknowledgements

The project was a collaborative effort between Simulations Plus, Inc. and GlaxoSmithKline and was funded by GlaxoSmithKline. The authors mourn the premature loss of Patricia K.P. Burnell of GlaxoSmithKline, an important member of the team who provided invaluable input and support.

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