Simulating the Disposition of Budesonide from Dry Powder Inhalers (DPIs) and Nebulizers

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OBJECTIVE

To simulate and predict the absorption and pharmacokinetics (PK) of budesonide following orally-inhaled (OIN) i.e. respiratory administration across multiple formulations and/or devices.

METHODOLOGY

All OIN formulations distribute both in the lungs and extra-pulmonary compartments such as oral cavity, larynx, pharynx, etc., the latter leading to swallowing and absorption through the gastrointestinal (GI) tract. The relative proportion of distribution in these two regions is a function of the formulation characteristics, device properties, administration conditions, and environmental factors. Thus, a robust mathematical model representing OIN formulations should contain appropriate respiratory, GI, and systemic components. In the current work, we apply a mathematical model to describe OIN administration of budesonide (a glucocorticosteroid with high local anti-inflammatory effects) across a variety of formulations and devices. The OIN component was modeled using a mechanistic physiologically based Pulmonary Compartmental Absorption & Transit (PCAT™) model that has been successfully used before. Recently, we developed a model describing disposition of budesonide in human subjects after intravenous (IV) and peroral (PO) doses using GastroPlus™ [1], which incorporates the proprietary Advanced Compartmental Absorption and Transit (ACAT™) model to simulate GI absorption (from oral doses). A PBPK model was used to describe the systemic PK. This model was used without further adjustment to describe the extra-pulmonary components of the OIN model. The **only fitted pulmonary parameter** across all formulation and device conditions was the first-order kinetic rate constant for systemic uptake from lung, fitted against plasma concentration-time (Cp-time) profiles following 0.8 mg of budesonide powder from a Turbuhaler™ device [2]. This model was then used without any further modification to predict the disposition of (a) 0.37 mg administrations of PulmoSphere™ powder from an Eclipse™ DPI both at low (29 L/min) and high (44 L/min) flow rates [2], and (b) 1 mg powdered budesonide from a Clickhaler™ [3]. In all cases, reported oropharynx and lung deposition values were used to obtain PCAT deposition fractions. The model was then used to predict the disposition of nanocrystalline budesonide from a PARI LC JetPlus™ Nebulizer [4]. In this case, reported particle sizes of 75–300 nm were used in conjunction with a flow rate of 8 L/min [4] to predict *in vivo* deposition in the lung and extra-pulmonary compartments using the ICRP66 deposition model [5].

RESULTS & DISCUSSION

Figure 1a shows the simulated Cp-time profile and observed values [2] for 0.8 mg budesonide administered as an aerosolized power via Turbuhaler™ to a mixed population (n = 10, F:M = 4:6, mean age = 34 y, mean weight = 74 Kg) using an unbound intrinsic liver CL of 1926.8 L/h (to account for higher CYP3A4 expression in females). Figure 1b & 1c show the same for 0.37 mg budesonide [2] administered as PulmoSphere from an Eclipse Dry Powder Inhaler (DPI) to the same mixed population at (b) high and (b) low airflow rates. For the PulmoSphere formulations the C_{max} is underpredicted, which could be attributed to aspects of the formulation itself and needs to be investigated further.

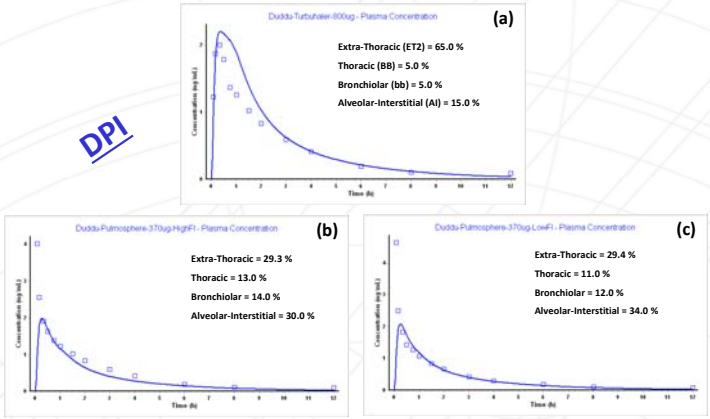

Fig 1. **Simulated(a)/ Predicted(b & c)** (line) and observed (points) Cp-time profile for administration of **aerosolized powder** of budesonide. (a) 0.8 mg via **Turbuhaler** and 0.37 mg via **Eclipse DPI** at (b) high & (c) low airflow rates. Deposition fractions were reported in [2] and are given in the inset.

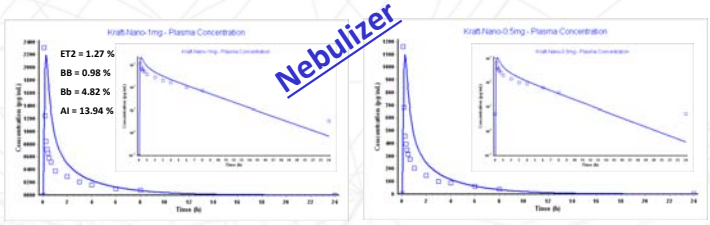

Fig 2. **Predicted** (line) and observed (points) [4] Cp-time profile for **nebulized** administration of **nanosuspensions** of (a) 0.5 and (b) 1 mg budesonide as 0.118 and 0.1158 h infusions, respectively, via **PARI LC JetPlus Nebulizer**. Deposition fractions were calculated using reported particle size and the ICRP66 model. Inset shows the same curves in a semi-logarithmic scale and the predicted deposition fractions.

Figure 2 shows the predicted Cp-time profile and observed values [4] for budsonide administered as nebulized nanocrystalline suspensions to a mixed population (n = 16, F:M = 3:13, mean age = 33y, mean weight = 76.8 Kg). In this case computational predictions of regional lung deposition fractions successfully captured the observed PK. Figure 3 shows the predicted Cp-time profile and observed values [3] for budesonide administered as aerosolized powder from DPI (Clickhaler) to a male population (n = 6, mean age = 28y, mean weight = not reported, predicted by PEAR Physiology). Reported [3] deposition fractions were used in the simulation.

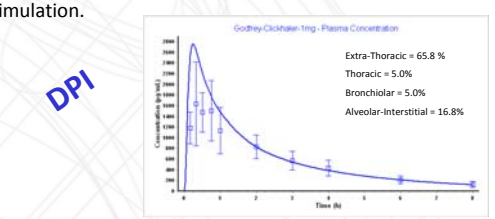

Fig 3. **Predicted** (line) and observed (points) [3] Cp-time profile for administration of 1 mg of **aerosolized powder** of budesonide via Clickhaler. Deposition fractions were reported in [3] and are given in the inset.

CONCLUSIONS

- **The GastroPlus PCAT model was successfully applied to simulate and predict the disposition of orally inhaled formulations of budesonide across multiple platforms (formulations and/or devices), including DPIs and nebulizers, without any further adjustments**
- **Assessing regional lung and extra-pulmonary deposition are critical as they significantly affect the PK of the drug and can be calculated from *in silico* models (ICRP66, NCRP, etc.), *in vitro* (ACI, NGI, etc.), or *in vivo* (gamma scintigraphy) measurements**

REFERENCES

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