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

S. R. Chaudhuri [1], V. Lukacova [2], W. S. Woltosz [2]
[1] Allergan, [2] Simulations Plus, Inc.

Purpose

To simulate and predict the human disposition of budesonide administered from various orally inhaled (OIN) devices with different formulation and deposition characteristics

Methods

A model describing disposition of budesonide (a glucocorticosteroid with high local anti-inflammatory effects) in human subjects after intravenous (IV) and oral (PO) doses was previously developed using GastroPlus™ 8.5. The Advanced Compartmental Absorption and Transit (ACAT™) model within GastroPlus was used to simulate absorption and a physiologically based pharmacokinetic model (PBPK) was used to describe the systemic PK. In the current work, the OIN component was modeled using a mechanistic physiologically based Pulmonary Compartmental Absorption & Transit (PCAT™) model that has been successfully used before. The only adjusted parameter was 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 Turbuhaler™. 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, and (b) 1 mg powdered budesonide from Clickhaler™. In all cases, reported oropharynx and lung deposition values were used to obtain PCAT deposition fractions. The model was also used to predict the disposition of nanocrystalline budesonide from a PARI LC JetPlus™ Nebulizer. In this case, reported particle sizes of 75 – 300 microns were used in conjunction with a flow rate of 8 liters/min to predict *in vivo* deposition.

Results

The developed ACAT/PCAT/PBPK model successfully predicted the behavior of all OIN doses of budesonide. The Cmax and AUC for the Pulmosphere formulation was slightly underpredicted. This could be due to incorrect interpretation of *in vivo* imaging data or unique aspects owing to the hollow nature of Pulmosphere.

Conclusion

The mechanistic and physiological nature of the model allowed succesfull prediction across various OIN platforms with varying particles sizes and deposition patterns. It is critical to measure and report particle sizes and/ or regional *in vivo* deposition since the they can significantly affect the disposition behavior of an OIN drug