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Modeling paradigms for orally inhaled drugs

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A major challenge for inhaled drug development is the development of physiologically relevant and predictive models. Modeling approaches applied to inhaled drugs include: a) Computational fluid dynamics; b) *in silico* methods and c) PK/PD modeling. With any route of administration, it is important to quantify the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug. There are several published examples,[1-5] some of them recent, of PK/PD models of inhaled drug distribution and effect. PK/PD can relate to local effects, such as improvement in lung function,[6] or to systemic effects such as hypokalemia.[5] Computer models for studying the lung deposition of inhaled aerosols have also been developed.[7-12]

Computational fluid dynamics

Computational fluid dynamics (CFD) is an emerging technology that is increasingly used in the field of inhaled drug lung deposition. The larynx to lower bronchioles are geometrically modeled in three-dimensional space, typically on the basis of CT scans or other medical images. Deposition and imaging approaches have been well described in the review by Scheuch, et al. 2010.[13] Kuttler, et al. 2014[14] used CFD in combination with data from the next generation impactor, particle image velocimetry and computed tomography (CT) to evaluate the extent of inhaled drug deposition at variable inhaler inclination angles and airway geometries. Jan De Backer, et al. 2014[15] have pioneered CFD methods for lung deposition modeling for orally inhaled products. They demonstrate how this approach can be used to compare lung deposition by two formulations of a fluticasone propionate/salmeterol HFA pressurized metered dose inhaler in stable asthma patients.

In silico methods

In silico modeling for pulmonary delivery can be performed during early development of an orally inhaled drug, utilizing non-clinical and early clinical PK data. This approach has to consider several factors, which include formulation effects (dosage form, particle size distribution, component interaction and excipients), physiochemical properties (solubility and permeability), dissolution,[16] physiological mechanisms such as mucociliary clearance, phagocytosis, lysosomal trapping, lung metabolism and potential for drug/drug interactions. In addition, the contribution of pulmonary and gastrointestinal absorption to systemic exposure after inhaled administration must be considered.

In silico modeling, together with investigations of the absorption rate and bioavailability of pulmonary-delivered drugs in relation to the drugs' molecular properties, is important to aid design of inhaled drugs for local and systemic action. A recent example, in which the commercially-available Gastroplus model[17] (in combination with a lung deposition model) was used to guide study interpretation, demonstrated the way an *in silico* approach was used to simulate systemic exposure for a poorly-soluble drug and to explain the lack of correlation between the delivered dose and the systemic exposure.

Compartmental PK/PD

Compartmental PK modeling approaches have been widely used to characterize systemic PK following orally-inhaled administration of low molecular weight drugs and biologics. A recent publication by Bartels, et al. 2013,[18] illustrates the way a population pharmacokinetics model was used to characterize lung absorption and disposition for glycopyrronium (NVA237); the model was used to support a once- daily dosage regimen. As stated by Bäckman, et al. 2014,[17] Weber and Hochhaus 2013[19] developed a compartmental model for simulating the PK of inhaled corticosteroids. This model included inter- and intra-subject variability clearance and allowed for simulation of PK trials of inhaled corticosteroids (ICSs) (budesonide, flunisolide, fluticasone propionate and triamcinolone acetonide). Prodrugs and soft-drugs are attractive platforms for the inhaled route because of their potential to maximize local exposure to the active moiety and minimize systemic exposure. Derendorf, et al. 2007[2] descri-bed PK/PD modeling for ciclesonide, an inactive prodrug converted to the pharmaco-

logically-active metabolite (desisobutyryl-cisclesonide), which raised some unique challenges because of its PK and PD profile. Renard, et al. 2011[20] described a model-based dose-response approach that was utilized to select the dose regimen for registration of indacaterol. Gaz, et al. 2012[21] developed a novel PK/PD compartmental approach in which the lung was represented by a 5-compartmental model, wherein the drug is assumed to be instantaneously well-stirred. This approach utilized a system of non-linear ordinary differential equations for simulation of PK/PD profiles.

Conclusions

Computational fluid dynamics has been used to obtain insight into patient-specific airflow patterns and regional distribution of inhaled drugs and consequently offers advantages over static imaging techniques, such as single photon emission computed tomography (SPECT) and computed tomography (CT). It has the potential to optimize inhalation treatment in a patient-centric way. *In silico* modeling for inhaled drugs is still in the early stages and further data are needed to support development and validation of these models. The PK/PD modeling methods have described characteristics of many inhaled drug classes, including long acting beta-agonists and inhaled corticosteroids and have been used for dose selection, evaluation of safety and efficacy, and assessment of risk/benefit profiles. PK/PD modeling in the drug development process is an essential tool to support regulatory submissions and registration and approval of inhaled drugs.

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