Sensitivity of Charcoal Block PK Metrics to Differences in Regional Deposition for Budesonide and Formoterol Fumarate Dihydrate

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Introduction

A physiologically based pharmacokinetic (PBPK) modeling approach was used to evaluate the potential for using the results of charcoal block pharmacokinetics (PK) studies to characterize product differences in regional deposition. The oral intake of charcoal in charcoal block PK studies aims to prevent gastrointestinal tract absorption, such that the resulting systemic PK data may be considered to be due to absorption through the lung exclusively. While it is clear that the in vivo data from a charcoal block PK study reflect total lung deposition (TLD), it is unclear to what extent the data reflect regional lung deposition. Two PBPK models were built to predict systemic PK for each of two active ingredients from a suspension-based metered dose inhaler (MDI) with the generic name budesonide; formoterol fumarate dihydrate inhalation metered aerosol. After the models were validated, simulations were conducted to test the sensitivity of systemic PK predictions to differences in regional deposition.

Materials and Methods

The software package GastroPlus® 9.8.3 (Simulations Plus, Inc., Lancaster, CA, USA) and the corresponding Pulmonary Compartmental Absorption & Transit (PCAT™) module were used to develop the PBPK models for budesonide and formoterol fumarate dihydrate. Formoterol fumarate dihydrate is the salt form prior to absorption and formoterol is the base form following absorption. A literature search was conducted to identify relevant model parameters, including fraction unbound in plasma, fraction unbound in lung tissue, blood-to-plasma ratio, octanol-water partition coefficient (log P), solubility, acid dissociation constant (pKa), diffusion coefficient, lung permeability, and oral bioavailability. For budesonide, intravenous (IV) PK data were collected from multiple literature sources, and then the GastroPlus module PKPlus™ was used to estimate distribution and clearance parameters based on pooled IV data. There were no IV data available for formoterol fumarate dihydrate, so PKPlus was used to estimate distribution and clearance parameters based on PK data from Eklund *et al.* [1] collected following inhalation administration of the reference listed drug (RLD) product, Symbicort, without a charcoal block.

For PK predictions following MDI administration, input parameters for dissolution, particle size distribution (PSD), and extrathoracic (ET) deposition were based on pooled aerodynamic particle size distribution (APSD) data collected for Contract 75F40119C10154 by the University of Florida and Emmace Consulting AB using three realistic mouth-throat (MT) models produced by the Oropharyngeal Consortium (OPC) and Virginia Commonwealth University (VCU) and three breathing profiles. Extrathoracic deposition and mean radius input values based on these APSD data ranged from 39.0 – 78.4% and 1.45 – 2.35 µm for budesonide, respectively, and 30.2 – 77.5% and 1.84 – 2.90 µm for formoterol fumarate dihydrate, respectively. For deposition in other regions, a central-to-peripheral deposition ratio (C/P) of 1 and exhaled fraction of 0.6% were assumed for the purposes of model development, based on in vivo imaging data from an MDI that includes budesonide, formoterol fumarate dihydrate, and glycopyrrolate [2]. The resulting input deposition values are given in Table 1 and Table 2. Model predictions were validated by comparing simulation results with PK data following administration of the RLD product from literature sources [1,3] and two regulatory data sources, with and without charcoal administration. After the models were validated, the deposition inputs were varied to identify potential sensitivity of PK results to differences in C/P and TLD.

Table 1. Input deposition fraction (DF) parameters for validation of budesonide PBPK model based on pooled realistic APSD data extrathorac DF data for VCU and OPC MT models.

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	71.0	14.200	7.100	7.100
	Medium	75.1	12.150	6.075	6.075
	Strong	78.4	10.500	5.250	5.250
VCU and OPC pooled medium	Weak	55.7	21.850	10.925	10.925
	Medium	55.5	21.950	10.975	10.975
	Strong	51.1	24.150	12.075	12.075
VCU and OPC pooled large	Weak	53.2	23.100	11.550	11.550
	Medium	39.0	30.200	15.100	15.100
	Strong	42.8	28.300	14.150	14.150

Table 2. Input deposition fraction (DF) parameters for validation of formoterol fumarate dihydrate PBPK model based on pooled realistic APSD data extrathorac DF data for VCU and OPC MT models.

MT Model(s)	Breathing Profile	Extra-thoracic DF (%)	Tracheo-bronchial DF (%)	Bronchiolar DF (%)	Alveolar-Interstitial DF (%)
VCU and OPC pooled small	Weak	66.0	16.700	8.350	8.350
	Medium	65.0	17.200	8.600	8.600
	Strong	77.4	11.025	5.513	5.513
VCU and OPC pooled medium	Weak	51.0	24.200	12.100	12.100
	Medium	48.8	25.300	12.650	12.650
	Strong	41.0	29.200	14.600	14.600
VCU and OPC pooled large	Weak	41.7	28.850	14.425	14.425
	Medium	30.2	34.600	17.300	17.300
	Strong	34.1	32.650	16.325	16.325

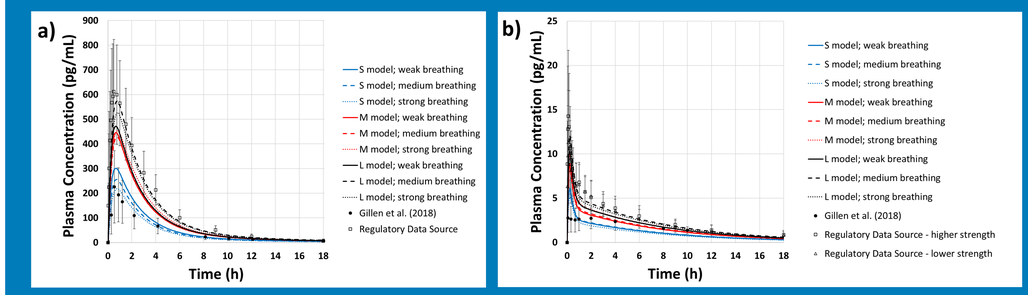

Figure 1. Plasma concentration predictions in a single subject intended to represent the population mean for a) budesonide and b) formoterol following two inhalations of the 0.16 mg/inh; 0.0045 mg/inh strength of the RLD product for budesonide; formoterol fumarate dihydrate inhalation metered aerosol, without a charcoal block. Predictions are compared with in vivo PK data from Gillen *et al.* [3] (n = 49) and a regulatory data source (n = 96), with error bars that show standard deviation. Model inputs are based on realistic APSD data collected with small (S), medium (M), and large (L) MT models under various breathing conditions, taken from Contract 75F40119C10154. In studies "Regulatory Data Source - lower strength" and "Regulatory Data Source - higher strength" the amount of formoterol fumarate dihydrate is the same for both strengths.

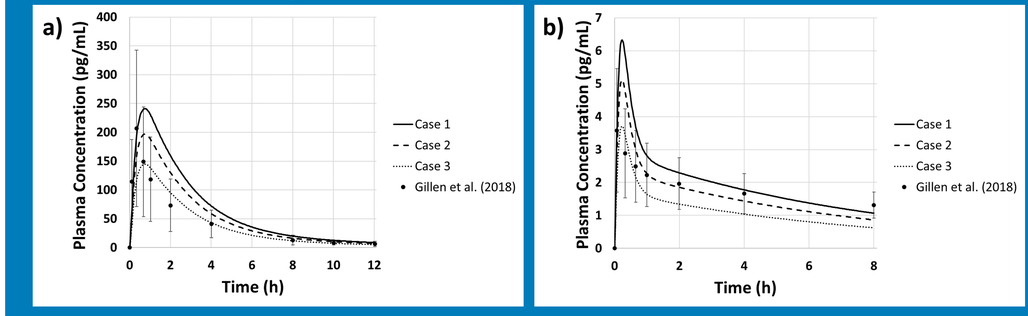

Figure 2. Plasma concentration predictions in a single subject intended to represent the population mean for a) budesonide and b) formoterol following inhalation administration of two actuations of the 0.16 mg/inh; 0.0045 mg/inh strength of the RLD product with charcoal co-administration for the small MT model and the strong breathing profile as compared with in vivo PK data from literature. Three cases were tested, where Case 1 is with C/P equal to 0.8 and TLD equal to 1.2 times the original value, Case 2 is with C/P equal to 1 and TLD equal to 1 times the original value, and Case 3 is with C/P equal to 1.25 and TLD equal to 0.75 times the original value.

Results and Discussion

Model validation of systemic PK predictions for budesonide; formoterol fumarate dihydrate inhalation metered aerosol showed that using the realistic APSD data to determine model inputs for extrathoracic deposition fraction and dissolution PSD described much of the range of PK variability observed for budesonide and formoterol. The results of model validation for budesonide and formoterol are given in Figure 1, where the variability in the PK metrics in the observed data from Gillen *et al.* [3] and a regulatory data source were well described by simulations generated using model inputs from three realistic MT models and three breathing profiles, supporting the clinical relevancy of the developed model.

Following model validation activities, simulations were conducted that varied C/P alone and C/P and TLD together, where for both active ingredients very little sensitivity was observed for C/P alone. However, it was hypothesized that C/P and TLD may be inversely correlated, and when a one-to-one inverse correlation was assumed for C/P and TLD, there was much larger sensitivity. Simulations were conducted to investigate the impact of a one-to-one inverse correlation between C/P and TLD on PK metrics, where the results visualized in Figure 2 and given in Table 3 show considerable sensitivity.

Table 3. Predicted values of maximum plasma concentration (C_{max}), area under the plasma concentration time curve from time 0 to time t (AUC_{0-t}), and area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) in a single subject intended to represent the population mean when a one-to-one inverse correlation is between central-to-peripheral deposition ratio (C/P) and total lung deposition (TLD) is assumed.

Active Ingredient	C/P	TLD	C_{max} (pg/mL)	AUC_{0-t} (pg-h/mL)	$AUC_{0-\infty}$ (pg-h/mL)
Budesonide	0.8	1.2	241.1	811.5	864.8
	1	1	197.0	662.1	705.5
	1.25	0.75	144.8	485.9	517.8
Formoterol Fumarate Dihydrate	0.8	1.2	6.3	16.3	24.7
	1	1	5.1	13.2	19.9
	1.25	0.75	3.7	9.5	14.5

Conclusion

Two PBPK models were developed to predict PK for each active ingredient following administration of budesonide; formoterol fumarate dihydrate inhalation metered aerosol. Model validation showed that by using parameter inputs based on in vitro realistic APSD data, simulation results reflected in vivo systemic PK data reasonably well for both active ingredients. A one-to-one inverse correlation was assumed between C/P and TLD, where predicted PK metrics following product administration with a charcoal block showed sensitivity to the combined effect on regional lung deposition. However, to apply these conclusions for regulatory purposes, further research is needed to address the remaining scientific gaps, which includes experimental verification of the assumed reverse relationship between C/P and TLD for budesonide and formoterol fumarate dihydrate under in vivo conditions as well as uncertainty with respect to the sources of PK variability. Regional deposition modeling is expected to be a useful means of better understanding the actual relationships between C/P and TLD for each active ingredient.

References

1. Eklund A, Tronde A, Johannes-Hellberg I, Gillen M, Borgström L. Pharmacokinetics of budesonide and formoterol administered via a series of single-drug and combination inhalers: four open-label, randomized, crossover studies in healthy adults. Biopharm Drug Dispos 2008, 29: 382-95.
2. Usmani O, Roche N, Wahab E, Israel S, Jenkins M, Trivedi R, Dorinsky P, Aurivillius M. A scintigraphy study of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in patients with moderate-to-very severe chronic obstructive pulmonary disease. Respir Res 2021, 22: 261.
3. Gillen M, Forte P, Svensson JO, Lamarca R, Burke J, Rask K, Nilsson UL, Eckerwall G. Effect of a spacer on total systemic and lung bioavailability in healthy volunteers and in vitro performance of the Symbicort®(budesonide/formoterol) pressurized metered dose inhaler. Pulm Pharmacol Ther 2018, 52: 7-17.

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