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Population Pharmacokinetics of (R)-Albuterol Following Inhaled Levalbuterol or Racemic Albuterol via a Hydrofluoroalkane Metered Dose Inhaler in Pediatric and Adult Asthma Patients

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ABSTRACT

Background: Levalbuterol (LEV), the (R)-enantiomer of racemic albuterol (RA), is approved for the treatment or prevention of bronchospasm in patients ≥4 years of age via metered dose inhaler (MDI). A population pharmacokinetic (PPK) model for (R)-albuterol following inhaled LEV or RA was developed, and the magnitude and variability of systemic exposure in pediatric and adult asthma patients were assessed.
Methods: Data were pooled from 81 pediatric and 551 adult subjects (aged 4-81 years) enrolled in three Phase 3 clinical trials. Plasma drug concentrations (n=3791) obtained following the first dose and after 4 or 8 weeks of QID inhalations (90 µg LEV or 180 µg RA via HFA MDI) were modeled using NONMEM®. Subject covariates were evaluated with stepwise forward selection (α=0.05) and backward elimination (α=0.001).
Results: The PK of (R)-albuterol was described by a 2-compartment model with first-order absorption and elimination. A significant positive relationship was identified between body weight and both apparent clearance (CL/F) and central volume of distribution (V_c/F). Mean (SD) individual predicted CL/F and V_c/F for LEV were 60.6 (15.4) L/hr and 493 (158) L, respectively. No significant differences in (R)-albuterol exposure existed across the age range (4-81 years), although exposure was 13 to 30% lower in subjects receiving LEV compared to RA.
Conclusions: A PPK model describing (R)-albuterol PK in pediatric and adult asthmatics was developed that will enable prediction of (R)-albuterol concentrations for future exposure-response analyses.

INTRODUCTION

- Inhaled β_2-adrenergic receptor agonists are widely prescribed for the prophylaxis and treatment of bronchoconstriction in subjects with reversible obstructive airway disease.
- The predominant bronchodilator in current clinical use is the β_2-selective adrenergic agonist, albuterol (Proventil®). This compound is a 50/50 racemic mixture of two stereoisomers (R, S). The (R)-isomer, levalbuterol, has at least 100 times more binding affinity at β_2 receptors than the (S)-isomer.
- Levalbuterol (Xopenex®), the pure (R)-isoform, was previously approved as a nebulized inhalation solution indicated for prophylaxis and treatment of bronchoconstriction in adult and pediatric asthmatics.
- The current analysis focuses on creating a PPK model for (R)-albuterol following administration via a new hydrofluoroalkane (HFA) MDI formulation of LEV or via the pre-existing RA HFA formulation.

OBJECTIVES

Develop a PPK model to:

- Characterize the pharmacokinetic profile of (R)-albuterol in pediatric and adult subjects following inhalation administration of LEV or RA via an HFA MDI formulation.
- Facilitate a comparison of exposure to (R)-albuterol following administration of LEV vs. RA.
- Evaluate the influence of patient characteristics on (R)-albuterol pharmacokinetics by identifying and quantifying statistically significant relationships between subject descriptors and key PK parameters.

METHODS

Study Design/Data

- Data from three randomized, multi-center, placebo- and active-controlled, double-blind, parallel-design Phase 3 clinical trials in adult and pediatric asthma patients were pooled.
- Dosing regimen: inhaled doses of 90 µg levalbuterol or 180 µg racemic albuterol four times daily (QID) delivered via an HFA MDI.
- Duration of treatment: 4 weeks in pediatrics, 8 weeks in adults.
- PK sampling design:
  - 1st dose: pre-dose, 1-2, and 4-6 hrs post-dose
  - After 4 or 8 weeks of QID dosing: pre-dose and 0.25, 0.5, 1, 2, 4, and 8 hrs post-dose

Pharmacostatistical Model

- Both one- and two-compartment PPK models were evaluated using the First-Order Conditional Estimation (FOCE) method with interaction in NONMEM® version 5, level 1.1.
- Interindividual variability (IIV) was estimated using an exponential error model.
- Residual variability (RV) was described using an additive plus proportional error model.

Subject Covariate Analysis

- Covariates examined: body weight, age, body surface area, creatinine clearance, gender, and race.
- Covariates were evaluated for inclusion into the final PPK model by univariate stepwise forward selection followed by backward elimination procedures.
  - Statistical significance was determined by a change in the minimum value of the objective function of ≥3.84 (α=0.05, 1 d.f.) during forward selection and ≥10.83 (α=0.001, 1 d.f.) for backward elimination.

Model Verification

- Goodness-of-fit for each NONMEM® analysis was assessed by:
  - Scatterplots of population and individual predicted vs. measured concentrations
  - Scatterplots of weighted residuals vs. predicted concentrations and time since last dose
  - %SEMs of PK parameter estimates
- Individual percent prediction error calculations were used to determine the accuracy (IPE%) and precision (|IPE%|) of the PPK model.

RESULTS

Data

- A total of 3791 (R)-albuterol plasma samples from 81 pediatric (4-11 years of age) and 551 adult patients (12-81 years of age) were utilized in this analysis.
- 429 patients (377 adults) received LEV and 203 patients (174 adults) received RA.
- Summary statistics of patient demographic information is provided in **Table 1**.
- Scatterplots of (R)-albuterol plasma concentrations versus time (**Figure 1**) demonstrate that PK profiles were similar between adults and pediatrics receiving either LEV or RA.

Final PPK Model

- A linear, two-compartment model with first-order absorption and elimination best described the (R)-albuterol concentration data. Final parameter estimates are provided in **Table 2**.
  - Separate K_a terms were estimated for adults and pediatric patients.
  - Relative bioavailability (F_1) was parameterized using the steady-state data from the 1st Phase 3 trial in adults as a reference (F_1=1).
  - IIV and IOV were utilized to characterize the between-subject random variability in F_1 and the random variability in F_1 between evaluation visits within each subject, respectively.
  - Residual variability was described using an additive plus proportional error model.
- Body weight was a significant predictor of both apparent clearance (CL/F) and apparent central volume of distribution (V_c/F), with these relationships being described by linear and power functions, respectively. The equations for computing the typical values of each population PK parameter are shown in **Equations 1** and **2** below.

$$TVCL_j\ (L/hr) = 59.1 + 0.477 \cdot (Wtkg_j - 74.8) \quad (1)$$

$$TVV_j\ (L) = 527 \cdot (Wtkg_j / 74.8)^{0.361} \quad (2)$$

Where:
$TVCL_j$ = the typical value of apparent clearance for the j^{th} patient;
TVV_j = the typical value of apparent central volume of distribution for the j^{th} patient; and
$Wtkg_j$ = the body weight (kg) of the j^{th} patient (centered around a median of 74.8 kg)

- Based upon individual model-predicted PK profiles and derived noncompartmental parameters (**Table 3**), exposure was predicted to be modestly lower in patients receiving LEV compared to RA. The magnitude of this effect was greater in pediatric subjects than in adults.
- No significant differences in (R)-albuterol exposure existed across the age range (4-81 years).

Model Verification

- IPE%: mean (SD) was 8.9% (29.3), with a median (range) of 2.9% (-47.4 to 473).
- |IPE%|: mean (SD) was 16.9% (25.6), with a median (range) of 9.96% (0.0 to 473).
- Goodness-of-fit plots are provided in **Figure 2**.

Table 1: Baseline Demographic Characteristics for Patients in PK Analysis Dataset

Covariate*	Adults (n=551)	Pediatrics (n=81)	90 µg LEV (n=429)	180 µg RAC (n=203)	Total (n=632)
Age (months)	433.7 (192.4) [145.0–981.0]	106.9 (28.1) [50.0–143.0]	393.9 (211.1) [50.0–964.0]	387.4 (209.6) [53.0–981.0]	391.8 (210.5) [50.0–981.0]
Weight (kg)	80.8 (22.3) [35.8–167.5]	37.1 (15.2) [14.5–89.4]	75.5 (26.0) [14.5–155.6]	74.5 (26.0) [20.0–167.5]	75.2 (26.0) [14.5–167.5]
BSA (m²)	1.95 (0.30) [1.25–3.01]	1.18 (0.29) [0.65–1.97]	1.86 (0.39) [0.65–2.86]	1.84 (0.39) [0.79–3.01]	1.85 (0.39) [0.65–3.01]
CrCL (mL/min)	133.6 (43.7) [49.6–310.6]	103.9 (31.3) [41.9–198.4]	129.5(43.6) [46.9–298.4]	130.5 (43.4) [41.9–310.6]	129.8 (43.5) [41.9–310.6]
Gender, n (%)					
Males	258 (47)	52 (64)	210 (49)	100 (49)	310 (49)
Females	293 (53)	29 (36)	219 (51)	103 (51)	322 (51)
Ethnicity, n (%)					
Caucasian	396 (71.9)	44 (54.3)	300 (69.9)	140 (69.0)	440 (69.6)
Black	99 (18.0)	23 (28.4)	81 (18.9)	41 (20.2)	122 (19.3)
Asian	13 (2.4)	2 (2.5)	8 (1.9)	7 (3.4)	15 (2.4)
Hispanic	47 (6.4)	12 (14.8)	34 (7.9)	13 (6.4)	47 (7.4)
Other	8 (1.5)	0 (0)	6 (1.4)	2 (1.0)	8 (1.3)

* Values for continuous variables presented as Mean (SD) [Min–Max]

Table 2: Parameter Estimates and Standard Errors for the Final PPK Model

Parameter	Population Mean		Magnitude of IIV[a] (%CV)	
	Final Estimate	%SEM	Final Estimate	%SEM
K_a (1/hr) – Adult Subjects (≥12 years)	6.28	7.8	67.60	17.4
K_a (1/hr) – Pediatric Subjects (<12 years)	3.08	15.4	74.63	30.7
F_1 (Levalbuterol)				
Pediatrics	0.550	11.9		
Adults (Study 051-355)	0.707	7.2	24.31	33.5
Adults (Study 051-353)	0.725	6.6		
F_1 (Racemic Albuterol)				
Pediatrics	0.830	15.1		
Adults (Study 051-355)	1.01	11.3	34.50	20.4
Adults (Study 051-353, SD[b] Visit)	0.880	6.4		
CL/F (L/hr)	59.1	14.6	39.50	23.8
V_c/F (L)	527	6.5	48.06	13.6
V_p (L)	506	25.1	69.35	22.2
Q (L/hr)	100	9.7		
Power Term for Body Weight on V_c/F	0.361	27.2		
Slope Term for Body Weight on CL/F (L/hr/kg)	0.477	26.4		
Interoccasion Variability in F_1 (%CV)				
Pediatrics	46.69	20.5		
Adults (Study 051-355)	35.21	18.1		
Adults (Study 051-353), Levalbuterol	32.71	15.7		
Residual Variability[c,d] (RV)				
Ratio of Additive/Proportional RV Components (σ_2/σ_1)	35.2	27.5		
Additive RV Component (σ_2)	0.0455	10.7		

[a] Interindividual variability
[b] Refers to visit after single dose of levalbuterol; Data from Visit 6 (Study 051-353) were utilized as the reference for bioavailability (F_1=1).
[c] Residual Variability (%CV) = $\sqrt{(IPRED^2 + (\sigma_2/\sigma_1)^2] \cdot \sigma_1^2)} \div IPRED \times 100\%$
[d] Magnitude of Residual Variability ranged from 21.99 to 21.33 %CV for individual predicted concentrations (IPRED) of 25 to 900 pg/mL.

Table 3: Mean (SD) Steady-State Non-Compartmental Pharmacokinetic Parameter Estimates Derived from Individual Model-Predicted PK Profiles

Study Population	Parameter	Randomized Treatment	
		Levalbuterol	Racemic Albuterol
Adult subjects (≥12 years)	C_{max} (pg/mL)	199.61 (108.56)	238.61 (130.57)
	T_{max} (hr)	0.54 (0.16)	0.54 (0.16)
	$AUC_{(0\text{-}6)}$ (pg·hr/mL)	692.41 (414.03)	800.70 (416.36)
Pediatric subjects (<12 years)	C_{max} (pg/mL)	162.48 (88.49)	237.73 (151.26)
	T_{max} (hr)	0.76 (0.35)	0.80 (0.43)
	$AUC_{(0\text{-}6)}$ (pg·hr/mL)	578.93 (307.42)	825.27 (506.04)

Figure 1: Scatterplots of (R)-Albuterol Concentration-Time Data

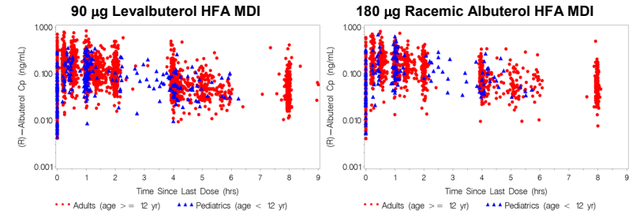
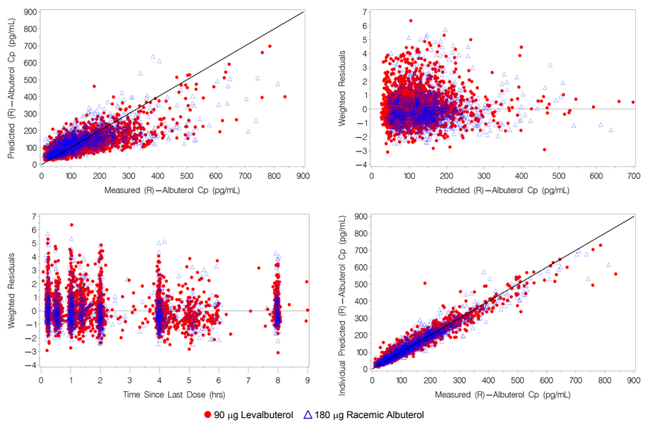


Figure 2: Goodness-of-Fit Plots for the Final PPK Model



CONCLUSIONS

- The pharmacokinetics of (R)-albuterol after administration of either Levalbuterol HFA MDI or Racemic Albuterol HFA MDI are linear and are adequately described using a two-compartment model with the inhaled drug administration modeled as a first-order absorption process in both pediatric and adult subjects.
- Following forward selection and backward elimination, body weight was found to be a significant predictor of both apparent clearance and central volume of distribution. No other covariates were determined to be statistically significant.
- Exposure to (R)-albuterol was lower in subjects receiving Levalbuterol HFA MDI compared to Racemic Albuterol HFA MDI, approximately 13% lower in adolescents and adults aged 12 years and older, and approximately 30% lower in children aged 4 to 11 years.

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