Population Pharmacokinetic Modeling for Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder in a Bioequivalence Study

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INTRODUCTION

- Advair Diskus, as a combination of fluticasone propionate (FP) and salmeterol xinafoate (SX) dry powder inhaler, is an important treatment for asthma and chronic obstructive pulmonary disease (COPD).
- Batch-to-batch variability has been reported for Advair Diskus.
- Few studies have reported the population pharmacokinetics (PK) of inhaled FP and SX.
- This work explored the population PK of inhaled FP and SX, with the aim to develop a model simulation platform that can accurately represent the product PK with potential batch variability.

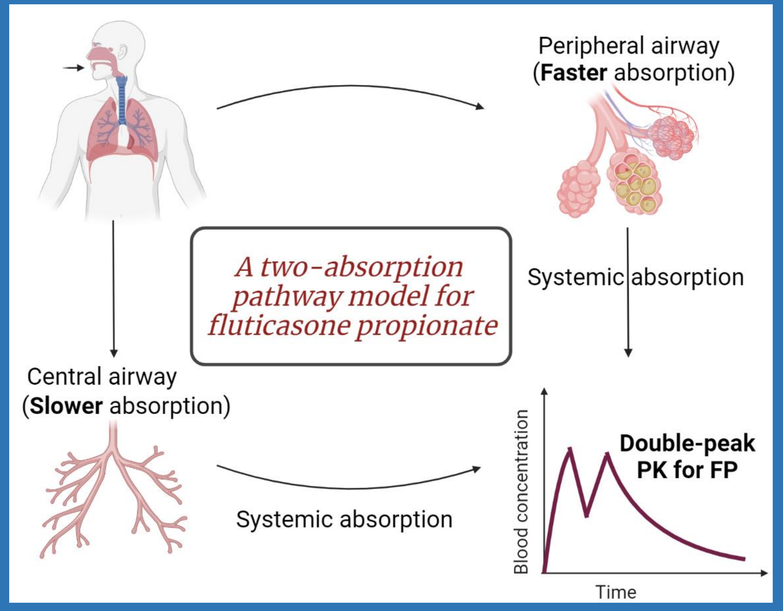
METHOD

- PK data from sixty healthy subjects administered two batches each of reference (R) and test (T) products of Advair Diskus (100/50 µg inhalation: denoted as R1, R2, T1, T2) in a crossover study were leveraged.
- Non-linear-mixed-effects modeling was used to characterize the population PK of FP and SX for each batch using Pumas v1.0.5 (Baltimore, MD).
- Various structural models and residual error models were evaluated.
- A two-stage approach was used in the estimation due to the high variability of the data. First, the individual PK parameters for each batch were estimated. Then, using the individual parameters, the population mean for each batch was estimated by adding batch as a fixed covariate effect.
- Visual predictive check (VPC) and quantitative predictive check (QPC) were used to qualify the simulation model platforms.

RESULTS

- A two-compartment model best captured the FP disposition profile (Table 1). FP individual absorption profiles were highly variable, and most subjects had systematic double peaks (Supplemental Figure S1). A sequential mixed zero-order and first-order absorption with lag time model best characterized FP absorption kinetics (Middle figure).
- A two-compartment model with first-order absorption kinetics best characterized the SX data (Table 2).

Pharmacokinetics of inhaled fluticasone propionate (FP) and salmeterol xinafoate (SX) are well characterized.*



* Middle picture shows FP model; SX model is not shown (see text).

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Exploratory analysis, VPC and QPC plots are in the supplemental material (scan the barcode)

RESULTS

Table 1. FP PK parameters

Parameters	R_1	R_2/R_1	T_1/R_1	T_2/R_1
Clearance (CL/F)	616 L/hour	0.82	0.93	0.95
Central volume (V_c/F)	2673 L	0.85	0.68	0.84
Intercompartmental clearance (Q/F)	758 L/hour	0.79	0.78	0.73
Tissue volume (V_t/F)	7802 L	0.82	0.65	0.80
Peripheral lung fraction (f_p)	61%	1.21	1.17	1.25
Duration for central lung (dur_c)	0.03 hour	3.84	2.01	1.59
Duration for peripheral lung (durp)	0.08 hour	0.89	0.84	0.84
Absorption rate constant (k_a)	4.3 /hour	0.9	1.05	1.02
Lagging time (t_{lag})	0.20 hour	1.53	1.57	1.53
Additive error	0.3 mg/L	-	-	-
Proportional error	11.4%	-	-	-

Table 2. SX PK parameters

Parameters	R_1	R_2/R_1	T_1/R_1	T_2/R_1
Clearance (CL/F)	377 L/hour	0.87	0.93	0.92
Central volume (V_c/F)	532 L	0.83	0.91	0.91
Intercompartmental clearance (Q/F)	1539 L/hour	0.76	0.98	0.91
Tissue volume (V_t/F)	2988 L	0.85	0.89	0.96
Absorption rate constant (k_a)	128 /hour	1.06	1.11	1.30
Proportional residual error	19.2%	-	-	-

DISCUSSION & CONCLUSION

This is the first study so far that estimated PK parameters of inhalation FP and SX separately for each batch. VPC and QPC plots demonstrated the adequacy of the final models, which are ready for the next simulation step.

ACKNOWLEDGEMENT & DISCLAIMER

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