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Population pharmacokinetic analysis of fexofenadine in Japanese pediatric patients

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Abstract A population pharmacokinetic analysis was conducted to characterize the pharmacokinetics of fexofenadine in Japanese pediatric patients (6 months through 16 years) with perennial allergic rhinitis or atopic dermatitis. The dataset was composed of 515 patients (including 109 adults), for a total of 1,080 concentration–time points. The analysis was performed with NONMEM using the SAEM method. Several structural models and residual error models were evaluated. The relationship between the individual estimates and the potential covariates was then investigated: demographic and pathophysiologic characteristics were tested as potential model covariates (forward selection method). The qualification of the model was performed using visual predictive check and bootstrap. A two-compartment disposition model with first-order absorption best fitted the data. The inter-individual variability was modeled through an exponential error model for all parameters (except for k_a for which no inter-individual term could be estimated), while a proportional error model

was used to model the residual variability. The final model included two covariates on elimination clearance and one on the intercompartmental clearance. CL/F was related to BSA and patient's age (expressed in months) Q/F was also related to BSA. Once the model was correctly qualified, exposure parameters such as C_{max} and AUC_{τ} were computed and compared between each age sub-group and between Japanese and Caucasians patients. These comparisons did not reveal any major difference (less than 50 %) between subgroups.

Keywords Population pharmacokinetics · Fexofenadine · Allegra · Pediatric · Japanese

Introduction

Fexofenadine HCl (Allegra[®]) is an antihistamine with selective peripheral H₁-receptor antagonist activity developed for allergic diseases. In Japan, it was approved for the indications of allergic rhinitis, urticaria and pruritus associated with skin diseases (eczema/dermatitis, pruritus cutaneous, atopic dermatitis). It is marketed at recommended doses of 60 mg twice daily for adults and children aged 12 years or older and 30 mg twice daily for children aged 7–11 years.

From studies in adults, fexofenadine appears to be rapidly absorbed after single or multiple oral administrations with a maximum plasma concentration observed 1–3 h after dosing. The absolute bioavailability is estimated to be at least 33 %. The apparent volume of distribution is large (5.4–5.8 L/kg) and the plasma protein binding is around 60–70 %. Fexofenadine is poorly metabolized (5 % of the total oral dose) and is mainly excreted in faeces via biliary excretion (80 and 11 % of the total dose in faeces and in

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urine, respectively). The apparent total body clearance is 48–58 L/h [1]. Fexofenadine is a probe substrate for the efflux transporter P-glycoprotein (P-gp) and for various uptake transporters, including human hepatic OATPB3; it is neither an inducer nor inhibitor of transporter activity at therapeutic doses [2]. In a previous pharmacokinetic (PK) study [3] conducted on 213 patients (77 children aged from 6 months to 12 years and 136 adults), race was explored and did not show any impact on the PK of fexofenadine.

A dry syrup formulation was developed to facilitate dosing of Allegra® in the pediatric Caucasian population. To evaluate this dry syrup formulation (15 and 30 mg twice daily doses) in Japanese pediatric patients 6 months through 11 years of age, two Phase III studies were conducted. Exposures were to be computed and compared to those of Caucasians to verify the proposed dose adjustment. As the number of samples collected per patient was limited in these studies (one or two samples), the Population Pharmacokinetic (PopPK) technique was used to characterize the PK of fexofenadine in this population and to compute individual patients' exposures.

While some PopPK analyses have already been made on Caucasian patients [3], this analysis is the first one performed on Japanese pediatric patients. This paper presents the results of this PopPK model. In a second step, individual patients' exposures computed from this model are compared between the different dosing groups to show the similarity of pediatrics' exposures to adults' ones, hence demonstrating the appropriateness of the proposed dosing algorithm, established on the basis of patients' age and weight. Results of Japanese patients are finally compared with those of Caucasians, as described in the paper from Krishna et al. [3].

Materials and methods

Study design

Two open-label, uncontrolled 4-week studies were conducted in pediatric patients: one in the treatment of perennial allergic rhinitis, the other one in patients with atopic dermatitis, for a total of 210 Japanese patients from 6 months to 11 years (381 concentrations–time points). The dosage of fexofenadine, given as a dry syrup formulation, was 15 mg twice daily for pediatric patients aged from 6 months up to less than 2 years, and older than 2 years but weighing less than 10.5 kg, and 30 mg twice daily for pediatric patients 2–11 years of age. Two blood samples per patient have been performed for determination of plasma fexofenadine concentrations: one at week 2 and one at week 4. Data from a previous PopPK analysis were also added: in this previous analysis, 298 Japanese patients

aged from 7 to more than 16 years (594 concentrations–time points) were included. The dosage of fexofenadine, given as tablets, was 30 mg twice daily for 8 days for 7–11 years, and 60 mg twice daily for 8 days for 12 years or more. Two blood samples per patient were performed after the morning dose of the study drug on day 8: 3 h after administration and 3–9 h after administration. Data from seven healthy Japanese volunteers (105 concentration–time points) obtained after 7-day twice-daily repeated dosing of 60 mg fexofenadine were also included. Overall, the total data set was composed of 515 subjects, for a total of 1,080 fexofenadine plasma concentrations (ranging from 1.2 to 6096 ng/mL). Demographic characteristics of the patients are presented in Table 1.

The clinical studies were conducted complying with the Declaration of Helsinki and related Japanese regulatory guidelines. The studies were initiated and conducted after getting an approval of the institutional ethical committee at each institute. Due to the age of the patients, the informed consent was obtained from the parents or the legal representative.

Model building

The PopPK analysis was performed with the NONMEM® [4] computer program (version 7.1.2) running on a LINUX cluster of multi-processor computers [5]. The First Order Conditional Estimation (FOCE) and the Stochastic Approximation of the Expectation–Maximization (SAEM) methods were evaluated; SAEM was selected for the model building process, as it was found to be the most stable method: the covariance step was difficult to obtain with FOCE.

Selection of the pharmacostatistical model

Initially the population parameters describing the PK model were estimated without covariate effects. Different structural PK models (one- and two-compartment disposition models with first order absorption) and different error models (additive, proportional and combined) were evaluated to describe residual variability. The full non diagonal matrix (ω block) and the different combinations of η correlations and η s fixed to zero were evaluated.

Covariates inclusion

The influence of potential covariates was assessed. The baseline values of age (in months), body weight (WGT), body surface area (BSA) and creatinine clearance (CL_{cr}) were tested as continuous potential covariates, together with dose and plasma levels of alanine aminotransferase (ALT), alkaline phosphatase (ALK), aspartate aminotransferase

Table 1 Demographic characteristics (baseline values) of the patients included in the population pharmacokinetic analysis

| Covariate or characteristic | Total dataset | Infants <2 Years | Children ≥2 to <7 Years | Children ≥7 to <12 Years | Adolescents ≥12 to <16 Years | Adults ≥16 Years |
|-------------------------------------|---------------|------------------|-------------------------|--------------------------|------------------------------|------------------|
| Mean (SD) values | | | | | | |
| Age (years) | 14.1 (13.8) | 0.564 (0.501) | 4.26 (1.37) | 9.00 (1.31) | 13.2 (1.13) | 37.2 (12.6) |
| Body weight (Kg) | 35.8 (18.9) | 9.25 (1.85) | 17.3 (3.79) | 30.9 (7.94) | 50.8 (12.7) | 57.2 (11.4) |
| Body surface area (m ²) | 1.14 (0.429) | 0.420 (0.0619) | 0.704 (0.111) | 1.07 (0.162) | 1.49 (0.214) | 1.61 (0.183) |
| Aspartate aminotransferase (UI/L) | 22.6 (12.1) | 41.3 (13.5) | 28.4 (4.75) | 19.0 (7.01) | 15.9 (6.73) | 20.4 (14.2) |
| Alanine aminotransferase (UI/L) | 19.8 (7.90) | 22.3 (11.3) | 13.8 (5.69) | 20.1 (7.29) | 21.6 (4.57) | 20.9 (8.54) |
| Alcaline phosphatase (UI/L) | 573 (371) | 0 (0) | 720 (151) | 835 (206) | 724 (357) | 202 (57.0) |
| Lactate dehydrogenase (UI/L) | 225 (58.2) | 309 (55.3) | 252 (37.1) | 232 (41.0) | 200 (41.6) | 173 (42.4) |
| Bilirubin (μmol/L) | 8.75 (4.91) | 5.08 (2.15) | 5.04 (1.81) | 7.76 (3.01) | 11.5 (4.63) | 12.5 (6.08) |
| Total protein (UI/L) | 64.2 (22.8) | 0 (0) | 71.0 (4.18) | 72.0 (6.73) | 72.1 (3.88) | 72.1 (4.19) |
| Creatinine (μmol/L) | 40.3 (15.9) | 17.1 (2.73) | 27.0 (5.26) | 37.9 (6.60) | 49.2 (10.2) | 57.8 (14.5) |
| Creatinine clearance (mL/min) | 171 (43.0) | 211 (35.3) | 195 (31.0) | 176 (27.7) | 179 (32.9) | 116 (30.8) |
| Number of patients (%) | | | | | | |
| Phase III study #1 (%) | 108 (21.0 %) | 7 (12.7 %) | 50 (61.7 %) | 51 (29.5 %) | – | – |
| Phase III study #2 (%) | 102 (19.8 %) | 48 (87.3 %) | 31 (38.3 %) | 23 (13.3 %) | – | – |
| Previous PopPK study (%) | 305 (59.2 %) | – | – | 99 (57.2 %) | 97 (100 %) | 109 (100 %) |
| Males | 276 (53.6 %) | 30 (54.5 %) | 54 (66.7 %) | 99 (57.2 %) | 59 (60.8 %) | 34 (31.2 %) |
| Females | 239 (46.4 %) | 25 (45.5 %) | 27 (33.3 %) | 74 (42.8 %) | 38 (39.2 %) | 75 (68.8 %) |
| Japanese (%) | 514 (99.8 %) | 55 (100 %) | 80 (98.8 %) | 173 (100 %) | 97 (100 %) | 109 (100 %) |
| Non Japanese (%) | 1 (0.194 %) | – | 1 (1.23 %) | – | – | – |
| Total number of patients | 515 | 55 | 81 | 173 | 97 | 109 |

(AST), lactate dehydrogenase (LDH), total bilirubin (TBIL) and total protein (TPRO). Sex and study were tested as categorical variables. All potential covariates were added individually to the model (forward selection method). Covariates effects were introduced into the population model using different functions: linear, power, exponential and allometric function. For the allometric functions, covariate effects were fixed (with 0.75 exponent for clearance and one for volume) and centered with 70 as recommended for pediatric data [6–8], or centered with the median weight value of the population. All the functions were tested at each step of the building model. A decrease of objective function value (OFV) of at least 3.84, associated with a *P* value <0.05 with one degree of freedom, was required and a decrease in the interindividual variability of the pharmacokinetic parameters and in σ value (which summarizes the unexplained variability on the estimated pharmacokinetic parameters) was expected.

In a last step, both individual and population parameters were re-estimated considering the relationship with the covariates. Each accepted covariate was deleted in turn from the proposed final model (backward elimination). An increase in OFV of at least 10.8, associated with a *P*-value <0.001 with one degree of freedom, was required for statistical significance to account for multiple testing and the large dataset and hence for the re-inclusion of the covariate.

Model validation

At each step of the model building process (i.e., each step of the pharmacostatistical model building and refinement, and each step of the covariate model building), GoF plots were used to evaluate the quality of the PopPK model. Several acceptance criteria (successful minimization of the algorithm, covariance phase completed without any warning message, significant digit greater than three, no correlation between parameter estimates larger than 0.95 and relative standard error [%RSE] lower than 50 %) were to be reached to consider the model as acceptable.

Bootstrap

The robustness of the model and the accuracy of parameters estimates (standard error computation) were assessed using a bootstrap method [9]. The entire procedure was undertaken in an automated fashion. From the original dataset of *n* patients, 500 bootstrap sets of *n* individuals were drawn with replacement (re-sampling). For each of the 500 bootstrap sets, the PopPK parameters were estimated. With the 500 estimates of each PopPK parameter, the corresponding mean, median, standard deviation, 2.5 and 97.5th percentiles were estimated.

Visual predictive check

The visual predictive check (VPC) [10] and the prediction corrected visual predictive check (pcVPC) [11], which is more suitable to data following adaptative designs such as dose adjustments, were used to evaluate the performance of the final model. These approaches, based on simulations from the model and the underlying design of the observed data, are a graphical comparison between the observed data and prediction intervals derived from the simulated data. In pcVPC, the dependent variable was prediction corrected: the variability coming from binning across independent variables was removed by normalizing the observed and simulated dependent variable based on the typical population prediction for the median independent variable in the bin. The pcVPC was used to evaluate the performance of the final model at steady state as a function of time (in both linear and logarithmic scales) but also as a function of the covariates included in the PopPK model.

Computation of individual exposures

From the population parameters, individual PK parameters, single dose and steady state exposure parameters (maximum [C_{\max} , $C_{\max,ss}$] and minimum [C_{\min} , $C_{\min,ss}$] concentrations, and area under the concentration–time curve between two drug intakes [AUC_{τ} , $AUC_{\tau,ss}$]) were estimated for each patient. Exposure variables were then plotted given the covariates included in the model to evaluate the magnitude of the covariate effect and compared to values observed in adults. Comparisons were also performed with Caucasian patients [3].

Results

Population model

The pharmacostatistical model was a two-compartment disposition model parameterized in terms of an absorption constant (k_a , 1/h) characterizing the first-order absorption process from the depot to the central compartment, which was described by an apparent distribution volume $V_c/F(L)$. The peripheral compartment was related to the central one by an inter-compartmental clearance Q/F (L/h) and described by an apparent distribution volume $V_p/F(L)$. The elimination process from the central compartment was defined by an elimination clearance CL/F (L/h). The inter-individual variability was modeled through an exponential model for all parameters (except for k_a for which no inter-individual term could be provided), while a proportional error model was used to model the residual variability. Three covariates significantly decreased the objective function and the inter-individual variability of the PK parameters:

- (i) CL/F was related to BSA and patient's age (expressed in months) according to: $CL/F = \theta_2 \times \left(\frac{BSA}{1.124}\right)^{\theta_6} \times \frac{AGE(\text{months})}{\theta_8 + AGE(\text{months})}$, where 1.124 is the median BSA value in the dataset,
- (ii) Q/F was also related to BSA according to: $Q/F = \theta_3 \times \left(\frac{BSA}{1.124}\right)^{\theta_7}$,
- (iii) V_c/F was related to weight according to: $\frac{V_c}{F} = \theta_4 \times \left(\frac{WGT}{70}\right)$.

For V_p/F , no relationship with any covariate led to a significant decrease of OFV. The backward deletion performed in the last step of the model development process led to WGT covariate deletion (iii) from the full model. The final PopPK parameters and their relationship to covariates are presented in Table 2, together with the model parameters obtained before covariates' inclusion. The relationship between individual estimates of CL/F and covariates retained in the model are given in Fig. S1 Supplementary material.

Validation of the model

All the acceptance criteria were reached.

Computation of standard error of estimates using bootstrap

The robustness of this final model and the accuracy of parameter estimates (standard error computation) were assessed using a bootstrap method. The bootstrap was performed on the total data set using the parameters of the final model as initial estimates. From the total data set (i.e., 515 patients), 500 runs were launched and 480 successful runs (96 %) were obtained. For each successful run, the PopPK parameters were estimated and the corresponding mean, standard deviation, 2.5 and 97.5th percentiles were estimated for each parameter. The median parameter estimates obtained from these bootstraps were similar to those of the final PopPK parameters (Table 2).

Visual predictive check

The VPC and pcVPC were used to evaluate the performance of the final model at steady state. The results of the simulations performed for pcVPC (one thousand samples time by patients) are presented in Fig. 1 and revealed a good predictive ability of the model.

Computation of individual pharmacokinetic parameters

Once the model validated using the previously described approaches, individual PK parameters (CL/F , V_c/F , Q/F and V_p/F), single dose and steady state exposure variables

Table 2 Population pharmacokinetic parameters obtained before and after covariates inclusion

| Parameter | No covariates | | Final model with covariates | | | Bootstrap on final model ^a | |
|--|------------------|-------|-----------------------------|------|-------------------------|---------------------------------------|-----------------|
| | Estimate | %RSE | Estimate | %RSE | [95 % CI] | Median estimate | [95 % CI] |
| Typical value of CL/F (θ_2 , L/h) ^b | 38.9 | 3.00 | 44.8 | 3.48 | [41.7; 47.9] | 44.8 | [42.1; 48.4] |
| Effect of BSA on CL/F (θ_6) ^b | NA | NA | 0.649 | 12.6 | [0.485; 0.812] | 0.647 | [0.479; 0.788] |
| Effect of age on CL/F (θ_8) ^b | NA | NA | 7.33 | 36.1 | [2.04; 12.6] | 7.38 | [3.25; 14.3] |
| Typical value of Vc/F (θ_1 , L) | 15.3 | 24.2 | 26.3 | 16.4 | [17.7; 34.9] | 27.0 | [16.5; 37.6] |
| Typical value of Q/F (θ_3 , L/h) | 5.85 | 11.4 | 8.25 | 8.51 | [6.85; 9.66] | 7.70 | [5.93; 10.5] |
| Effect of BSA on Q/F (θ_7) ^c | NA | NA | 1.60 | 12.2 | [1.21; 1.99] | 1.58 | [1.14; 2.10] |
| Typical value of Vp/F (θ_4 , L) | 221 | 39.6 | 185 | 17.1 | [122; 249] | 190 | [127; 331] |
| Typical value of ka (θ_5 , 1/h) | 0.272 | 0.660 | 0.280 | 1.36 | [0.273; 0.288] | 0.276 | [0.262; 0.310] |
| | Estimate (CV%) | %RSE | Estimate (CV%) | %RSE | [95 % CI] (Shrinkage %) | Median estimate | [95 % CI] |
| Inter-individual variability | | | | | | | |
| $\omega_{CL/F}^2$ | 0.241 (49.1) | 12.0 | 0.0798 (28.3) | 15.9 | [0.0545; 0.105] (26.7) | 0.0801 | [0.0571; 0.107] |
| $\omega_{Vc/F}^2$ | 2.95 (172) | 16.6 | 1.25 (112) | 21.7 | [0.708; 1.79] (55.3) | 1.28 | [0.818; 2.19] |
| $\omega_{Q/F}^2$ | 0.435 (66.0) | 33.5 | 0.172 (41.4) | 9.90 | [0.138; 0.206] (82.7) | 0.155 | [0.0378; 0.416] |
| $\omega_{Vp/F}^2$ | 0.561 (74.9) | 38.8 | 0.350 (59.2) | 19.2 | [0.216; 0.485] (90.0) | 0.310 | [0.114; 0.715] |
| ω_{ka}^2 | Fixed to 0.00001 | | | | | | |
| Residual variability | | | | | | | |
| σ^2 | 0.131 (36.2) | 7.55 | 0.139 (37.3) | 7.00 | [0.119; 0.158] (18.3) | 0.138 | [0.120; 0.158] |

θ and ω are the PopPK parameters (θ) and the variance of their associated inter-individual variability (ω), σ is the associated variance of the residual (intra-individual) error variable (ϵ)

F bioavailability, %RSE percentage of relative standard error (100 % * SE/Estimate), NA not applicable, 95 % CI 95 % confidence interval

^a Bootstrap results obtained on 480 successful runs

^b The expression of clearance including covariates effects is: $CL/F = \theta_2 \times \left(\frac{BSA}{1.124}\right)^{\theta_6} \times \frac{AGE(months)}{\theta_8 + AGE(months)}$

^c The expression of the intercompartmental clearance including covariate effect is: $Q/F = \theta_3 \times \left(\frac{BSA}{1.124}\right)^{\theta_7}$

(C_{max} , $C_{max,ss}$, C_{min} , $C_{min,ss}$, AUC_{τ} and $AUC_{\tau,ss}$) were estimated for each patient. Main descriptive statistics in the different subpopulations are given in Table 3 as a function of the covariates included in the model. As an illustration, $AUC_{\tau,ss}$ are represented in Fig. 2. Similar trends were observed with $C_{max,ss}$ and $C_{min,ss}$.

Discussion

The population model developed in this analysis accurately predicted fexofenadine plasma concentrations observed in Japanese pediatric patients suffering of perennial allergic rhinitis or atopic dermatitis. The available potential sources of variability on the population parameters were extensively investigated.

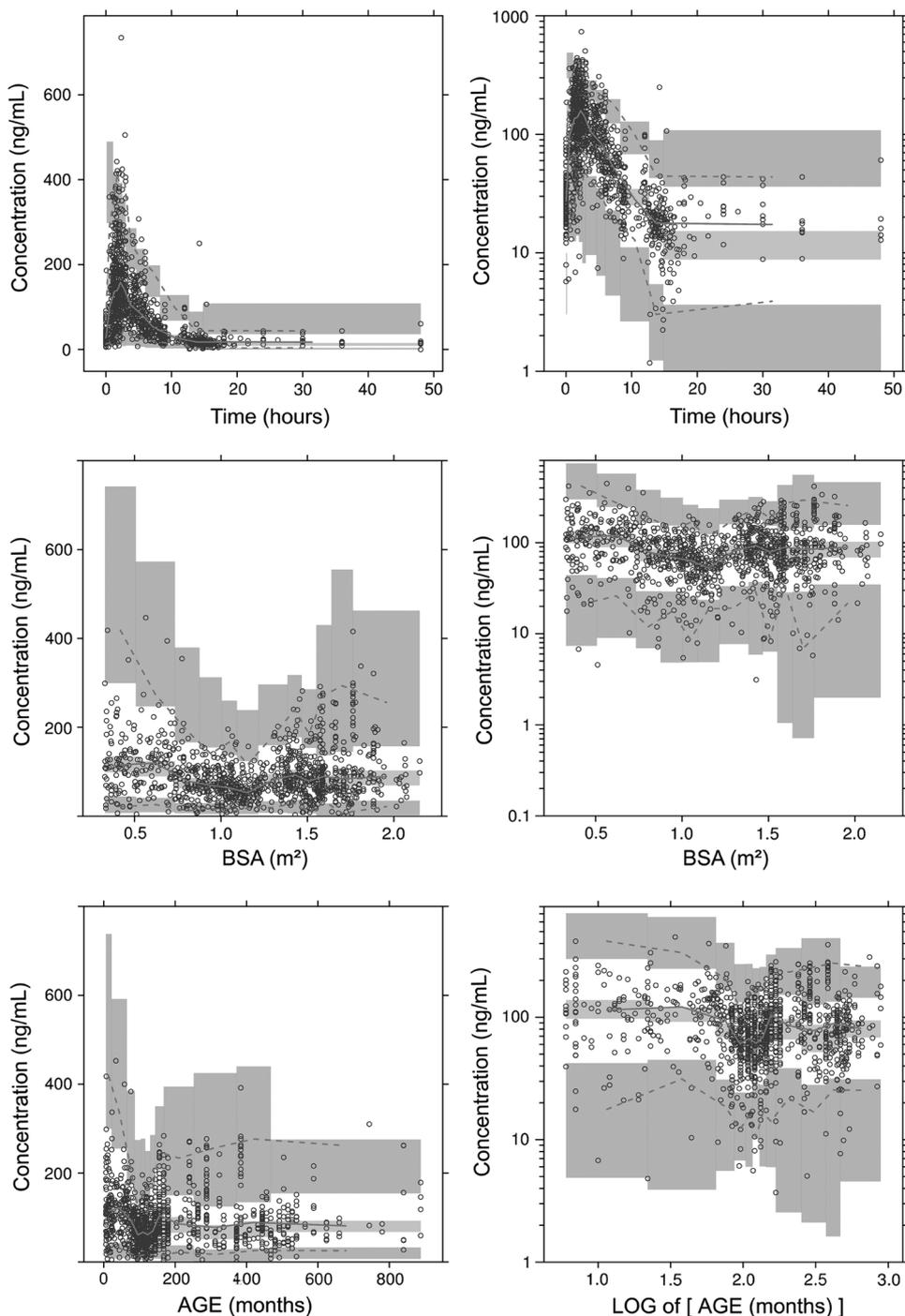
Two covariates were included in the model on CL/F and Q/F: BSA and age (in months) were included on CL/F, BSA was also included on Q/F. This inclusion allowed an important decrease of the unexplained interindividual variability on both clearances (from 49.1 to 28.3 % for CL/F and from 66.0 to 41.4 % for Q/F) but also on the two

distribution volumes. No covariate was included on Vc/F, Vp/F and ka.

In the paper of Krishna et al. [3], body weight was identified as a significant covariate of the model. In the current analysis, the OFV decrease was systematically more important after inclusion of BSA rather than body weight. As the main aim of the current study was to estimate as accurately as possible individual exposures, the covariate which allowed the better fit to the available data, i.e., BSA, was kept in the final model. As BSA is directly derived from body weight using the Dubois and Dubois [12], formula the impact of body weight is integrated in BSA.

In the end, the ‘body size’ measurement selected is of minor importance: while the dosing algorithm used in these clinical studies was adapted from the one proposed in Caucasians on the basis of age and body weight (but Japanese patients aged 0.5–2 years received only 15 mg dose whatever their body weight), fexofenadine dosage will finally be marketed without any dose adjustment to either body weight or BSA. Dose is only adjusted according to patient’s age in Japanese patients. The absence of side

Fig. 1 Prediction corrected visual predictive check as a function of time (*upper left: linear scale, upper right: log scale*) or of covariates included in the PopPK model (*middle left: BSA [linear scale], middle right: BSA [log scale], lower left: age [linear scale], lower right: age [log scale]*). Lines are 5, 50 and 95th percentiles of observations, areas are 95 % confidence intervals of these percentiles



effects, linked to the wide safety range of fexofenadine, confirmed this selected dosing regimen.

All %RSEs were lower than 20 % (except the age effect on clearance which was about 36 %). Probably due to the very sparse data available (only two samples per patient for the pediatric population), high values of η -shrinkage were observed (26.7–90.0 %). σ -shrinkage remained below 20 %.

Individual derived exposure variables estimated from the PopPK model were similar in infants <2 years

receiving 15 mg twice daily, in children ≥ 2 to <7 years receiving 30 mg twice daily, in adolescents' ≥ 12 to <16 years and in adults ≥ 16 years receiving 60 mg twice daily. Exposure variables were approximately 35 % lower in children ≥ 7 to <12 years receiving 30 mg twice daily according to CL/F values.

The comparison of the PopPK parameters obtained in Japanese and Caucasian children was only possible for individual values of elimination clearance and C_{\max}

Table 3 Mean (CV%) values of individual steady state exposures given by covariates included in the model

| | AUC _{τ,ss} (ng.h/mL) | C _{max,ss} (ng/mL) | C _{min,ss} (ng/mL) |
|---|-------------------------------|-----------------------------|-----------------------------|
| 15 mg dose (n = 56) | | | |
| By age | | | |
| Infants <2 years (n = 55) | 1,090 (46.2) | 155 (39.5) | 34.4 (112) |
| Children ≥2 to <7 years (n = 1) | 703 ^a | 111 ^a | 15.2 ^a |
| By BSA | | | |
| BSA ≤1.1249 ^b m ² (n = 56) | 1,080 (46.3) | 154 (39.5) | 34.0 (112) |
| BSA >1.1249 ^b m ² | No patient in this group | | |
| 30 mg dose (n = 253) | | | |
| By age | | | |
| Children ≥2 to <7 years (n = 80) | 1,060 (24.3) | 176 (27.9) | 25.8 (38.8) |
| Children ≥7 to <12 years (n = 173) | 710 (19.8) | 127 (21.4) | 16.7 (30.2) |
| By BSA | | | |
| BSA ≤1.1249 ^b m ² (n = 199) | 875 (28.1) | 151 (28.3) | 20.8 (41.1) |
| BSA >1.1249 ^b m ² (n = 54) | 621 (17.1) | 112 (20.2) | 15.1 (26.9) |
| 60 mg dose (n = 206) | | | |
| By age | | | |
| Adolescents ≥12 to <16 years (n = 97) | 1,150 (23.0) | 213 (19.8) | 28.4 (35.2) |
| Adults ≥16 years (n = 109) | 1,110 (28.2) | 200 (19.3) | 29.2 (48.3) |
| By BSA | | | |
| BSA ≤1.1249 ^b m ² (n = 3) | 1,280 (12.4) | 239 (22.6) | 28.2 (15.9) |
| BSA >1.1249 ^b m ² (n = 203) | 1,130 (25.9) | 206 (19.7) | 28.8 (43.0) |

^a Individual values

^b Median of the dataset

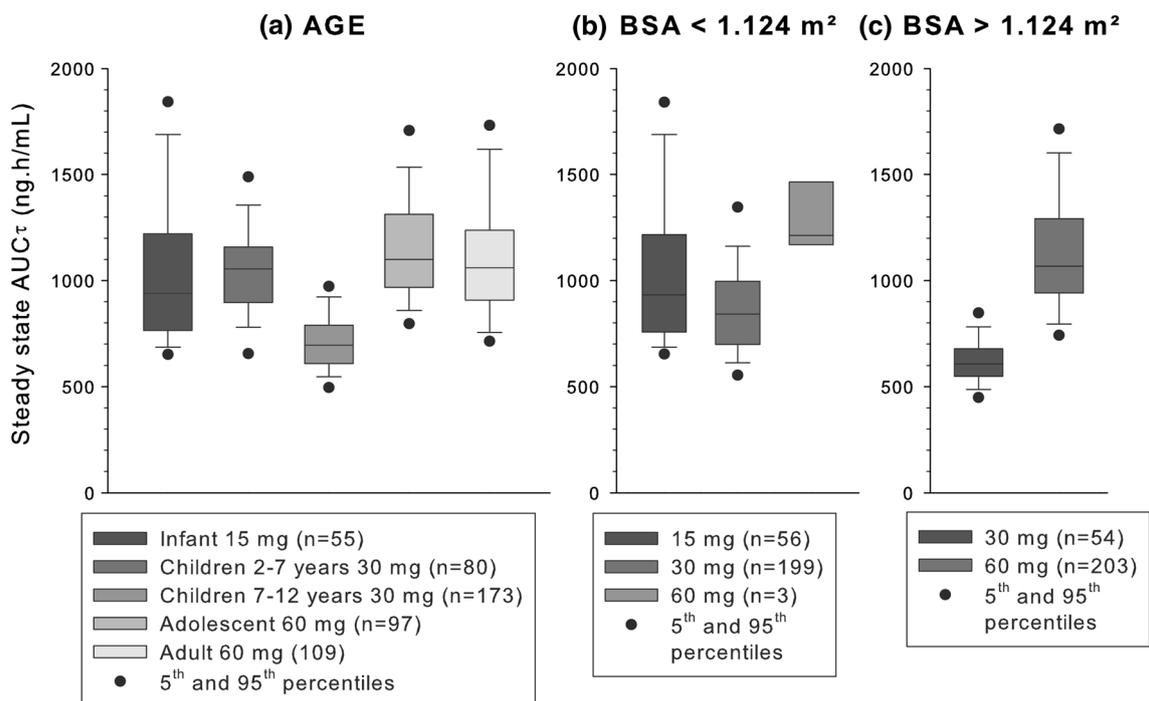


Fig. 2 AUC_{τ,ss} as a function of covariates included in the population pharmacokinetic model

Table 4 Mean (CV%) values of individual single dose exposures in Japanese and Caucasians patients

| Dose (mg) | Age | C _{max} (ng/mL) | | | CL/F (L/h) | |
|-----------|---------------------------------|--------------------------|------------------------------|--------------------|---------------------|---------------------|
| | | Japanese Raw values* | Japanese Normalized to 80 mg | Non-Japanese | Japanese | Non-Japanese |
| 15 | Infants <2 years | 130 (41) (n = 55) | 693 (41) (n = 55) | 972 (30) (n = 13) | 15.6 (30) (n = 55) | 14.9 (26) (n = 13) |
| 30 | Children ≥2 to <6 or 7 years** | 157 (29) (n = 80) | 419 (29) (n = 80) | 411 (25) (n = 21) | 29.9 (24) (n = 80) | 34.3 (25) (n = 21) |
| | Children ≥6 or 7 to <12 years** | 113 (22) (n = 173) | 301 (22) (n = 173) | 409 (36) (n = 14) | 43.9 (20) (n = 173) | 30.1 (27) (n = 14) |
| 60 | Adults ≥16 years | 175 (18) (n = 109) | 233 (18) (n = 109) | 208 (32) (n = 136) | 57.8 (25) (n = 109) | 53.6 (34) (n = 136) |

* C_{max} values for Japanese children converted from the values estimated for each dose to 80 mg dose

** 6 years in non-Japanese children and 7 years in Japanese children

obtained *after single dose* (Table 4), as results obtained in Caucasian children [3] do not provide any value for volume of distribution and steady state exposures. For these comparisons, C_{max} values for Japanese children obtained after administration of 15, 30 or 60 mg were converted in a linear manner to the 80 mg dose for which they were provided in [3].

As shown in Table 4, C_{max} values were 40 % higher in Caucasian than Japanese in children aged 0.5–2 years (972 vs. 693 ng/mL) while CL/F values were similar (14.9 and 15.6 L/h, respectively). As stated previously, Japanese patients aged 0.5–2 years received only 15 mg dose whatever their body weight, while Caucasian patients in the same age range but weighing more than 10.5 kg received 30 mg dose. However, about 1/4 of the Japanese patients aged 0.5–2 years weighted more than 10.5 kg. This could explain the higher mean C_{max} value on Caucasian patients.

No difference was seen in C_{max} and CL/F values when 30 mg was administered to Japanese children aged 2–7 years and to Caucasian children aged 2–6 years (419 and 411 ng/mL, and 29.9 and 34.3 L/h, respectively).

C_{max} values were 36 % higher in Caucasian than in Japanese children aged 6 or 7–12 years (409 vs. 301 ng/mL) with CL/F values 46 % higher in Japanese than in Caucasian children. This difference might be explained by the small number of Caucasian patients studied (n = 14) as compared to Japanese children (n = 173). Moreover, while Caucasian children were enrolled into a same single study, Japanese patients were enrolled into several studies; the inter-study variation could also explain such differences.

Last, C_{max} and CL/F values obtained in adults were also similar between Japanese and Caucasian patients.

Based on CL/F values, there was no major difference between Japanese and Caucasian across adults, adolescents and infants. Consequently, the difference observed in Japanese children aged 6 or 7–12 years do not seem to be explained by ethnic factors affecting metabolic or excretion systems.

CL/F in pediatric patients was 27 % (<2 years) and 51 % (2–6/7 years) of the adult patients' clearance.

Conclusion

The PopPK technique allowed estimating the PK of fexofenadine in Japanese pediatric patients despite the very low number of samples collected per patient.

The exposure parameters were in the same magnitude than those observed in adults and in Caucasian patients, except for the 30 mg BID dose given to patients aged 7–12 years.

These findings support the interest of the proposed dosing regimens in agreement with the dosing recommendations in Caucasians. These dosing regimens (twice daily doses of: (i) 15 mg for patients aged from 6 months up to less than 2 years, (ii) 30 mg for patients 2–11 years of age and (iii) 60 mg for 12 years or more) allowed obtaining adequate exposures across Caucasian and Japanese population, from pediatric to adult stage.

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Conflict of interest All the authors except Sonia Khier are Sanofi employees.

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