

Effects of Age and Sex on the Pharmacokinetics of Isavuconazole

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ABSTRACT

Objective: This Phase 1, open-label, parallel group, single-dose study evaluated the pharmacokinetics (PK) of isavuconazole after a single oral dose of isavuconazonium sulfate in healthy non-elderly (18–45 years) and elderly (≥65 years) male and female subjects.

Methods: Overall, 48 subjects were enrolled in the study (12 male, 12 female non-elderly and 12 male, 12 female elderly subjects). All subjects received a single oral dose of the prodrug isavuconazonium sulfate equivalent to 200 mg isavuconazole (fasting conditions). PK samples for isavuconazole plasma concentrations were collected pre-dose to 336 hours post-dose. Data was analyzed using population PK analysis.

Results: The initial model resulted in a 2-compartment model, with unique clearance (CL) values for each group (Table 1). Due to the similarity in CL values between non-elderly males and elderly males, male subjects were grouped together, while elderly and non-elderly female subjects remained as separate distinct groups. Further modeling resulted in a 2-compartment model with Weibull absorption function. No covariates were significant on exposure. CL values from the best model are presented in Figure 2. Total area under the concentration curve (AUC) was calculated using the standard formula ($AUC = F \cdot DOSE / CL$) based on the individual parameter estimates. Elderly females had the highest exposure of all groups studied compared with males (total AUC 138%, 90% CI: 118%, 161%) compared with non-elderly females (total AUC 147%, 90% CI: 123%, 176%) and non-elderly females had similar exposure compared with males (total AUC, 94%, 90% CI: 80%, 109%).

Conclusion: Population PK analysis showed that elderly female subjects had lower CL values for isavuconazole compared with all other subjects. However, the PK difference is not clinically relevant. Therefore no dose adjustments are recommended based on age or gender.

INTRODUCTION

- Isavuconazonium sulfate, the water-soluble prodrug of the broad-spectrum, triazole antifungal, isavuconazole (ISAV), was developed for the treatment of invasive fungal disease (IFD).
- Based on the results from Phase 3 clinical trials,^{1,2} isavuconazonium sulfate was approved by the US Food and Drug Administration for the treatment of adults with invasive aspergillosis (IA) and invasive mucormycosis, and by the European Medicines Agency for the treatment of adults with IA and adults with mucormycosis for whom amphotericin B is inappropriate.
- IFD cause considerable morbidity and mortality in the immunocompromised and have become a growing problem, because older adults are more likely to require transplantation, receive immunosuppressive drugs or chemotherapy for cancer.³
- A Phase 1 study was conducted to analyze the effect of age/gender on the pharmacokinetics (PK) of ISAV. The primary objective of this analysis was to determine the effect of age and gender on the PK of ISAV using population pharmacokinetic (PPK) analysis.

METHODS

Study design

- This was a Phase 1, open-label, parallel group, single dose study to evaluate the PK of ISAV in healthy non-elderly (18–45 years) and elderly (≥65 years) male and female subjects.
- All subjects received a single oral dose of isavuconazonium sulfate equivalent to 200 mg ISAV under fasting conditions.
- Plasma samples for ISAV PK analysis were collected pre-dose to 336 hours post-dose.

Analysis

- Using PPK, the concentration–time data in both elderly male and female and non-elderly male and female subjects were modeled.

- PPK analysis was carried out by nonlinear mixed-effects modeling using the software program NONMEM®, Version 7.2.
- Total area under the concentration curve (AUC) at steady state for individual subjects was calculated using the standard formula ($AUC = F \cdot DOSE / Clearance$) based on the individual parameter estimates from the best covariate model, where F is bioavailability.

RESULTS

Study population

- A total of 48 healthy adults were enrolled in the study including 12 male and 12 female non-elderly subjects and 12 male and 12 female elderly subjects.

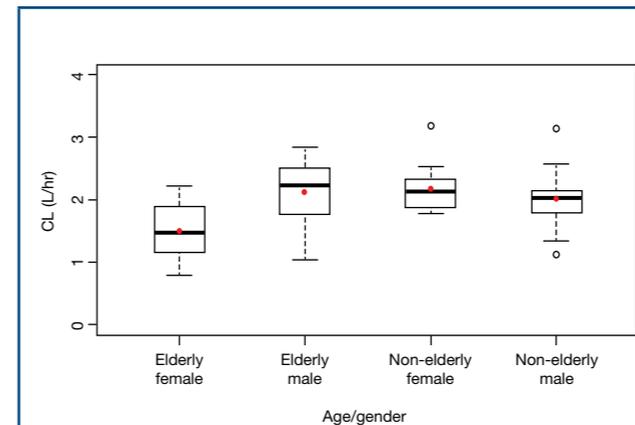
PPK outcomes

- Initial model resulted in a 2-compartment model, with unique ISAV clearance (CL) values for each study group (Table 1). The values are presented in Figure 1 as box and whisker plots.

Table 1. ISAV clearance values for different groups based on age and sex

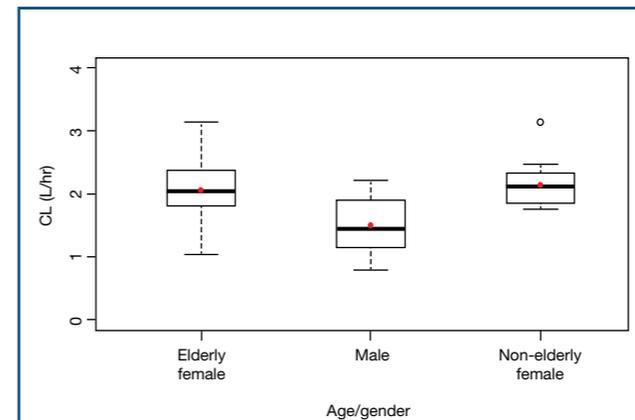
Parameter	Non-elderly male mean (SD)	Elderly male mean (SD)	Non-elderly female mean (SD)	Elderly female mean (SD)
CL (L/hr)	1.94 (0.52)	2.04 (0.52)	2.13 (0.39)	1.44 (0.43)

- Based on the initial modeling results, it can be seen that there is no difference in ISAV CL values between non-elderly male and elderly male subjects.
- Due to the similarity in CL values between non-elderly males and elderly males, male subjects were grouped into a single group, with elderly and non-elderly female subjects still treated as separate distinct groups.



Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; solid red circles are means; outliers are shown as open circles.

Figure 1. ISAV clearance values for different groups based on age and sex



Boxes represent median, 25th and 75th percentiles; whiskers represent range of maximum and minimum values within 1.5 × the interquartile range; solid red circles are means; outliers are shown as open circles.

Figure 2. Clearance values from the best model were similar for male and non-elderly female subjects

- Further model development processes resulted in a 2-compartment model with Weibull absorption function. The model fit the data adequately with no observable systemic bias. Typical population parameters, including covariate effects as well as most of the random variance parameters, were estimated with good precision. The shrinkage associated with CL was 5%.
- Figure 2 shows the CL values from the best model. From the figure it can be seen that CL values were similar for male and non-elderly female subjects.
- Statistical analysis of AUC for each group, showed elderly females had the highest exposure of all groups studied (Table 2).
- Non-elderly females had similar exposure to males.

Table 2. Statistical analysis of AUCs

Parameter	Comparison	Ratio (%)	90% CI of ratio
AUC	Elderly female vs. male	137.86	118.00, 160.95
	Elderly female vs. non-elderly female	147.42	123.27, 176.29
	Non-elderly female vs. male	93.52	80.10, 109.18

CONCLUSIONS

- From the PPK analysis, it can be seen that elderly female subjects had lower CL values and higher exposure compared with rest of the subjects.
- The pharmacokinetic difference in elderly females receiving ISAV are not considered to be clinically significant. Therefore, no dose adjustment of ISAV is required based on age and gender.

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DISCLOSURES

A.V. Desai, D. Kowalski, C. Lademacher, H. Pearlman, T. Yamazaki, and R. Townsend are employees of Astellas Pharma Global Development, Inc.