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No Dose Adjustment Necessary for Isavuconazole in Obese Patients

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ABSTRACT

Background: Isavuconazonium sulfate, the water-soluble prodrug of the broad-spectrum, triazole antifungal, isavuconazole (ISAV) was developed for the treatment of invasive fungal disease (IFD). The objective of this analysis was to determine if ISAV pharmacokinetics are different in obese vs. non-obese patients with fungal infections and if a dose adjustment is necessary in obese patients.

Methods: Patients from 3 clinical studies (SECURE, ACTIVE and VITAL) were combined for this analysis. 74 patients (~25 from each study) were classified as obese (BMI >30 kg/m^2) as described in the protocols for the 3 clinical studies. 144 non-obese patients (~2:1 ratio) were randomly selected from the 3 clinical studies (~48 from each study). Concentration–time data were analyzed using population pharmacokinetic model developed in NONMEM®. Obesity was investigated as the covariate of interest.

Results: A 2-compartment model with first order absorption and linear elimination fit the data adequately. Obesity was only significant on peripheral volume of distribution and no other parameter of interest. Area under the curve (AUC) was calculated using the standard formula (F*DOSE/Clearance), where clearance was obtained from the empirical Bayes' estimates for each individual patient. No apparent difference in AUC was observed between obese and non-obese patients (**Figure 1**). The geometric mean AUC in obese patients was 68 mg*hr/L as compared to 73 mg*hr/L in non-obese patients (P=0.17).

Conclusion: Due to similarity in exposures between obese and non-obese patients across 3 clinical studies, no ISAV dose adjustment is necessary for obese patients.

INTRODUCTION AND PURPOSE

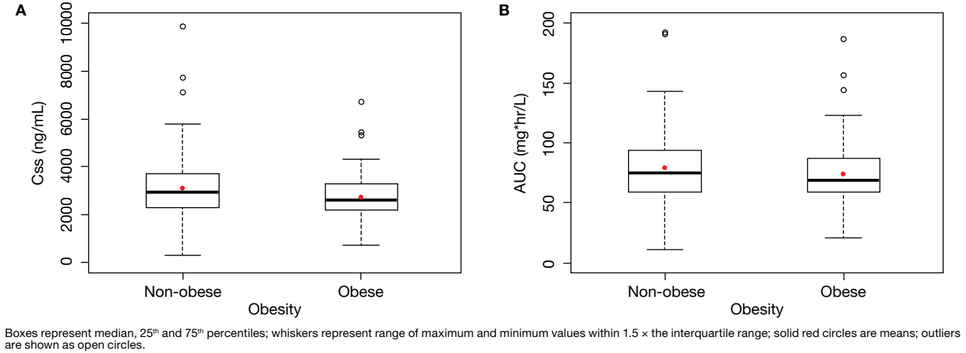
- Isavuconazonium sulfate, the water-soluble prodrug of the broad-spectrum, triazole antifungal, isavuconazole (ISAV), was developed for the treatment of invasive fungal disease (IFD).
  - Based on the results from Phase 3 clinical trials,[1,2] isavuconazonium sulfate was approved by the US Food and Drug Administration for the treatment in adults of invasive aspergillosis (IA) and invasive mucormycosis, and by the European Medicines Agency for the treatment in adults of IA and of mucormycosis in adults for whom amphotericin B is inappropriate.
- The pharmacokinetics of some other triazole antifungal agents may be altered in obese and overweight patients.[3,4]
- This post hoc analysis was performed to determine if ISAV pharmacokinetics is different in obese vs. non-obese patients with fungal infections and if a dose adjustment is necessary in obese patients.

METHODS

- Patient data were from 3 clinical studies: the SECURE study, in patients for primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi, the ACTIVE study, in patients with candidemia and other invasive *Candida* infections, and the VITAL study, in patients with invasive fungal disease caused by rare fungi, including mucormycosis.
- The dose for all 3 clinical studies was identical, with loading dose of 372 mg isavuconazonium sulfate (equivalent to 200 mg of ISAV) every 8 hours for 6 doses (48 hours) via oral or intravenous administration, followed by maintenance dose of 372 mg isavuconazonium sulfate (equivalent to 200 mg of ISAV) once daily via oral or intravenous administration starting 12 to 24 hours after the last loading dose.
- Data for obese and non-obese patients were combined for this analysis.
  - 74 patients (~25 from each study) were classified as obese as described in the protocols for the 3 clinical studies (BMI >30 kg/m^2).
  - 144 non-obese patients were randomly selected from the 3 clinical studies (~48 from each study), which provided an approximate 2:1 ratio between non-obese and obese patients.
  - 11 patients in the obese group and 13 patients in the non-obese group had a 24-hour concentration–time profile; the remaining patients in both groups had at least 1 trough concentration sample.
  - Concentration–time data were analyzed using population pharmacokinetic model developed in NONMEM® version 7.2.
  - Only obesity was investigated as the primary covariate of interest.
  - The area under the curve (AUC) was calculated using the standard formula (F*DOSE/Clearance), where F is bioavailability.
  - Clearance was obtained from the empirical Bayes' estimates for each individual patient.

RESULTS

- In total, 353 PK concentrations from non-obese patients and 213 concentrations from obese patients were part of the pharmacokinetic data set for analysis.
- A 2-compartment model with first order absorption and linear elimination fit the data adequately.
- There was no observable systemic bias in the developed model.
- Obesity was only significant on peripheral volume of distribution and no other parameter of interest.
- The estimates of clearance for obese and non-obese patients are presented in **Table 1**.
- No apparent differences in trough concentrations at steady state (Css) (P=0.053) and AUC (P=0.198) were observed between obese and non-obese patients (**Figure 1**).
- The geometric mean AUC in obese patients was 69 mg*hr/L as compared with 75 mg*hr/L in non-obese patients.



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. Box and whisker plot of Css values (A) and AUC values (B) versus obesity

Table 1. Estimated clearance values

Clearance (L/hr)	Non-obese patients	Obese patients
Arithmetic mean (SD)	2.98 (1.7)	3.20 (1.6)
Median	2.67	2.90
Geometric mean	2.71	2.94
10th–90th percentile	1.71–4.36	1.83–5.13

SD, standard deviation.

CONCLUSIONS

- The developed model fit the data adequately.
- There were no differences in exposure between obese and non-obese patients in the conducted clinical studies.
- The similarity in exposures between obese and non-obese patients across these 3 clinical studies strongly suggests that no dose adjustment is necessary for ISAV in obese patients.

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DISCLOSURES

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