PREDICTIONS OF IZAVUCONAZOLE SULFATE DOSEAGE IN PATIENTS AGED 6 MONTHS – <18 YEARS

BY PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING

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ABSTRACT

Objective: Identifying dosage regimens for “first-in-pediatric” clinical trials require use of prior information from efficacious and safe exposures in adults. The purpose of the following analysis was to predict the pediatric equivalent dose (PED) for patients between the ages of 6 months to 18 years of age using physiologically based pharmacokinetic (PBPK) modeling.

Methods: All simulations and adult data were completed using PBPK-Picasso & E3 BioBase Technology (Astellas, Northbrook, IL, USA). The adult data were drawn from patients between the ages of 18 years and older and consisted of 15 organs each. Organs were structured into the default small molecule mode of four compartments: interstitial, plasma, red blood cells, and intracellular space. The adult PBPK model was validated by matching observed adult concentrations after a single dose of 50 mg/kg of isavuconazonium sulfate in adults following single and multiple oral and IV administrations. A virtual pediatric population was created consisting of 15 organs each. Simulations assessed optimal doses of isavuconazonium sulfate based on age and weight.

Results: The target isavuconazonium AUC0–inf (180–360 mg·h/L) was derived from the P3 clinical study in adult patients with IA and other filamentous fungi. The exposures predicted by PBPK for children from 6 months to less than 18 years were similar to predictions from allometric scaling for children aged 2–<18 years. For ages 6 months to 1 year, a dose of 6 mg/kg is predicted to achieve similar exposures.

Conclusions: From the predictions, it can be concluded that either method (PBPK or allometric scaling) could be used to predict exposures in children more than 1 year old.

INTRODUCTION AND PURPOSE

Izavuconazole sulfate, the water-soluble prodrug of the broad-spectrum, triazole antifungal, isavuconazole, was developed for the treatment of invasive fungal disease (IFD).

Based on the results from Phase 3 clinical trials,1,2 isavuconazole sulfate was approved by the U.S. Food and Drug Administration for the treatment of adults with invasive aspergillosis (IA) and invasive mucormycosis,2 and by the European Medicines Agency for the treatment of adults with IA and adults with mucormycosis for whom amphotericin B is inappropriate.3

Simulations were performed to assist in direct dosing regimen for the initial pediatric clinical trial using allometric scaling for children more than 2 years old.4

However, no dosing information is available in pediatric patients less than 2 years old.5,6

The purpose of this analysis was to predict the pediatric equivalent dose (PED) for patients between the ages of 6 months to 18 years of age using physiologically based pharmacokinetic (PBPK) modeling.

PBPK is a frequently used method for predictions in children less than 2 years old as it applies to ontogeny of enzymes or renal function and other age-dependent physiological information, such as liver blood flow.

RESULTS

As shown in Figure 1, from the PBPK analysis, an isavuconazole sulfate dose of 10 mg/kg is predicted to achieve similar exposures. Figure 2 shows the allometric scaling pediatric dose range (100–233 mg·h/L) for the majority of patients more than 1 year old.

For patients aged 6 months to 1 year, a dose of 8 mg/kg predicts exposures comparable to those in adults after administration of the recommended clinical dosing regimen from the SECURE study in patients with IA.

The majority of the predicted exposures and mean exposures from the 1116 mg dose (equivalent to 600 mg of isavuconazole) in adults (233 mg·h/L, and 353 mg·h/L, respectively).

A proposed isavuconazole sulfate dose of 10 mg/kg is predicted to result in safe and efficacious steady-state exposures in patients aged 1–<18 years, which was similar to predictions from allometric scaling for patients aged 2–<18 years.

For subjects aged 6 months to 1 year, a dose of 6 mg/kg was predicted to achieve similar exposures.

From the predictions, it can be concluded that either method (PBPK or allometric scaling) could be used to predict exposures in children more than 1 year old.

These pediatric doses are currently being tested in clinical trials to confirm the appropriate dose for pediatric patients.

CONCLUSIONS

METHODS

All simulations (adult and pediatric) were completed using PBPK-Picasso version 6.3 (Bayeir Technology, Leverkusen, Germany) and the PBPK-Picasso model, which incorporates the whole-body PBPK model for adults and children consisting of 15 organs.

Objectives: To determine the appropriate dose for pediatric patients.

Organ sizes were drawn from the P3 clinical study in adult patients with IA and other filamentous fungi. The exposures predicted by PBPK for children from 6 months to less than 18 years were similar to predictions from allometric scaling for children aged 2–<18 years. For ages 6 months to 1 year, a dose of 6 mg/kg is predicted to achieve similar exposures.

The predictions from allometric scaling are presented in Table 2. From the predictions, it can be concluded that either method (PBPK or allometric scaling) could be used to predict exposures in children more than 1 year old.

These pediatric doses are currently being tested in clinical trials to confirm the appropriate dose for pediatric patients.

The predictions from allometric scaling are presented in Figure 2. The exposures predicted by PBPK for children from 6 months to less than 18 years old were similar to predictions by allometric scaling for children from 2 to less than 18 years old.

REFERENCES


DISCLOSURES

Amit V Desai, Christopher Lademacher, PE, and SL. Kovanda are employees of Astellas Pharma Global Development, Inc. SL. Kovanda is a current member of the Pediatric Critical Care Working Group of the Infectious Diseases Society of America (IDSA).

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Table 1. AUC values from in vitro studies

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<thead>
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<th>Dose (mg/kg)</th>
<th>AUC0–12h (mg·h/L)</th>
<th>AUCinf (mg·h/L)</th>
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<td>20</td>
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<td>2.305</td>
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<tr>
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<tr>
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Table 2. AUC values from studies

<table>
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<tr>
<th>Dose (mg/kg)</th>
<th>AUC0–12h (mg·h/L)</th>
<th>AUCinf (mg·h/L)</th>
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</thead>
<tbody>
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<td>1</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>10</td>
<td>1000</td>
<td>2000</td>
</tr>
</tbody>
</table>

*Table 1 values are from in vitro studies (mg·h/L).

*Table 2 values are from in vivo studies (mg·h/L).