Physiologically-Based Pharmacokinetic (PBPK) Modeling of Oral Absorption of 5-flucytosine to Support Development of a Sustained-Release Formulation for Treatment of Cryptococcal Meningoencephalitis

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ACNOWLEDGEMENTS

This project is funded by the European & Developing Countries Clinical Trials Partnership (EDCTP) programme supported by the European Union (grant EDCTP2-CO- 2516), with additional funding from the Swiss Agency for Development and Cooperation (SDC), Médecins Sans Frontières International, and other private foundations and individuals. The findings and conclusions contained herein are those of the authors and do not necessarily reflect positions or policies of the aforementioned funding bodies.

RESULTS

The refined 5-FC PBPK model described the PK data in study 1 well (Figure 1), with absolute average fold error (AAFE) values for AUClim,lin and Ctrough of 1.13 for both parameters. Of the three SR formulations, the fastest release formulation (Formulation D) had the highest bioavailability (20%) relative to the IR tablet in study 1. Prolonged GET enables a longer time for absorption and the predicted relative bioavailability for Formulation D in fed state increased to 80%, still with the highest bioavailability of the three SR formulations. The estimated doses required for treatment D to be within the therapeutic target concentrations with a tri-daily dosing were approximately 6000 mg in fasted state and 5000 mg in fed state (Figure 2).

According to simulations, a dose of 6000 mg can be given as a first dose regardless of prandial state (if unknown for unconscious patients when admitted to the hospital) without exceeding the therapeutic Cmax concentration (Figure 3).

The PK data obtained from study 1 was used to further update and refine the legacy model. PBPK modeling was performed in PK-Sim v.9.1. Table 1. Predicted parameters for the IR and SR of 5-FC in fasted state and predicted parameters for the SR in fed state. Values are presented as mean ± SD.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IR - Fasted (Study 1)</th>
<th>SR - Fasted (Study 1)</th>
<th>SR - Fed (Study 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUClim (L/min/kg)</td>
<td>524±520</td>
<td>327±240</td>
<td>417±260</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>39.2±1.8 (second dose)</td>
<td>16.9±3.8</td>
<td>19.9±3.2</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>7.4±0.3 (second dose)</td>
<td>4.7±1.3</td>
<td>7.2±2.1</td>
</tr>
<tr>
<td>Relative bioavailability (%)</td>
<td>-</td>
<td>62</td>
<td>80</td>
</tr>
</tbody>
</table>

CONCLUSIONS

1. The estimated doses for 5-FC plasma concentrations to be within the therapeutic target with tri-daily dosing were approximately 5000 mg in fed state and 6000 mg in fasted state.
2. A loading dose of the SR formulation was not needed for it to be comparable to the IR formulation, according to the model.
3. The risk of exceeding the therapeutic safe range, due to uncertainties in prandial state, was predicted to be low, even at a higher starting dose (6000 mg).
4. The model will be refined based on data from study 2 and used in the subsequent step of the MIDO strategy, informing the design of a clinical Phase II study in CM patients.

REFERENCES


M1430-10-68