Population pharmacokinetic and time-to-event modelling of the antimalarial drug lumefantrine in young children with severe acute malnutrition

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Objective & Methods

Objectives: This study aimed to characterise the pharmacokinetic-pharmacodynamic properties of the antimalarial lumefantrine in children with severe acute malnutrition (SAM).

Methods: 131 SAM children and 266 non-SAM children with uncomplicated falciparum malaria were administered with lumefantrine every 12 hours for 3 days. Malnutrition status was characterised using standard WHO guidelines [1]. Dry blood spot capillary concentrations were measured using LC-MS/MS. Nonlinear mixed-effects modelling was performed to characterise the pharmacokinetic properties of lumefantrine. Parasitemia at the time of recurrent infection was used to determine the possible starting interval of the malaria erythrocytic stage [2]. Then, an interval-censoring time-to-event model was used to describe the events (re-infections).

Results

- Pharmacokinetic model
- The LLOQ data were modelled using the M6 method [3].
- Malnutrition associated covariates are highly correlated.
- Allometric function of body weight and enzyme maturation effects were added into the pharmacokinetic model as prior knowledge.
- Covariate evaluation was performed using stepwise covariate modelling and full covariate approach.
- The MUAC was the most significant covariate on the bioavailability.

- Effect of malnutrition status

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Conclusions

- The PK/PD properties of lumefantrine were characterized accurately.
- Pharmacokinetic model: Two-transit absorption model followed by two disposition compartments. Allometric scaling of body weight and enzyme maturation effects were included into the model.
- Pharmacodynamic model: Interval censoring time-to-event model.
- SAM children have a lower lumefantrine exposure than normal children.
- Bioavailability was reduced by 25% per cm reduction in mid-upper arm circumference.
- The time-to-event model could accurately predict the starting interval of the malaria erythrocytic stage.
- Lumefantrine dose adjustment is needed urgently in SAM children.

Final parameter estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population estimates (95% CI)</th>
<th>IC50 CI of estimates</th>
<th>%CV of BSV (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F (L/h)</td>
<td>7.03 (5.02-9.44)</td>
<td>6-12</td>
<td>25.5%</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>2.25 (1.54-3.36)</td>
<td>0-3.6</td>
<td>22.6%</td>
</tr>
<tr>
<td>V/F</td>
<td>1.62 (1.20-2.17)</td>
<td>0-2.5</td>
<td>28.2%</td>
</tr>
<tr>
<td>Q3/F</td>
<td>0.51 (0.37-0.70)</td>
<td>0.3-1.0</td>
<td>34.2%</td>
</tr>
<tr>
<td>V3/F</td>
<td>0.04 (0.02-0.07)</td>
<td>0.005-0.08</td>
<td>26.0%</td>
</tr>
</tbody>
</table>

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References: