PHARMACOKINETICS OF EFAVIRENZ DOSED ACCORDING TO THE WHO WEIGHT-BANDS IN CHILDREN IN UGANDA

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ABSTRACT

Background: Efavirenz (EFV) is commonly used in children over 5 years worldwide, but there is only limited pharmacokinetic (PK) information available in African children.

Methods: 41 HIV-infected Ugandan children aged 3-12 years on generic EFV plus 3TC-ABC were included in the substudy of the ARROW trial (www.arrowtrial.org). Once daily EFV dosing following WHO weight bands were 200/250/300/350 mg and 400 mg for children weighing 10-15/15-20/20-25/25-30 kg respectively, using EFV capsules or halved 600 mg tablets. Intensive plasma PK sampling for children weighing 40 kg or more and >24 hours after observed intake was repeated after 4 weeks and at the end of 36 weeks. A total of 54 children contributed PK data. Results: 3/41 children had evaluable PK profiles at PK1. A large inter- and intra-subject variability was found in EFV PK parameters compared with data from adults. There were no differences across weight-bands. Three sub-populations were identified from normal mixture modeling: 40% children with geometric mean AUC (95% CI) of 50.4 (91.7-139.5) mg·h/L at week 36, 27% children with AUC of 54.0 (80.8-120.0) mg·h/L, 33% children with AUC of 7.4 (5.5-8.7) mg·h/L at week 36.

RESULTS – DEMOGRAPHICS

Table 1: Baseline demographics of children in substudy of the ARROW trial

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N with or more evaluable PK</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>23 (59%)</td>
<td>39</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>19.5 (18.5-23.0)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>3-6 years</td>
<td>18 (46%)</td>
</tr>
<tr>
<td></td>
<td>7-12 years</td>
<td>21 (54%)</td>
</tr>
<tr>
<td>Weight-for-age, z-score</td>
<td>-1.41 (-2.12 to -0.65)</td>
<td></td>
</tr>
<tr>
<td>Height-for-age, z-score</td>
<td>-1.80 (-2.80 to -1.11)</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

• The high inter- and intra-subject variability in EFV PK parameters compared with data from adults but this was consistent across weight-bands.
• Three sub-populations were identified from normal mixture modeling: children with geometric mean AUC of 50.4 mg·h/L, 54.0 mg·h/L and 7.4 mg·h/L.
• Electronic supplementary material is available online at www.cell.com.

We thank all the patients and staff from all the centres participating in the ARROW trial.

REFERENCES


RESULTS - PHARMACOKINETICS - 1

A large inter- and intra-subject variability was found in EFV PK parameters (eg 81% and 28% for AUC\textsubscript{max} and AUC\textsubscript{0-24} respectively). Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake. A large inter- and intra-subject variability was found in EFV PK parameters (eg 81% and 28% for AUC\textsubscript{max} and AUC\textsubscript{0-24} respectively). Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake. A large inter- and intra-subject variability was found in EFV PK parameters (eg 81% and 28% for AUC\textsubscript{max} and AUC\textsubscript{0-24} respectively). Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake. A large inter- and intra-subject variability was found in EFV PK parameters (eg 81% and 28% for AUC\textsubscript{max} and AUC\textsubscript{0-24} respectively). Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake. A large inter- and intra-subject variability was found in EFV PK parameters (eg 81% and 28% for AUC\textsubscript{max} and AUC\textsubscript{0-24} respectively). Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake.

RESULTS - PHARMACOKINETICS - 2

• Children received once daily EFV dosed according to WHO recommendations (Table 1) as 50mg or 200mg capsules or halved 600mg tablets. At week 32, children were changed to AM intake of EFV if they were taking EFV PM. At week 36 after starting EFV twice daily, children received once daily PK sampling was repeated and an extra PK sample was drawn at 24 hours after observed intake.