• Nevirapine is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) widely used for treatment of HIV-infected adults and children [1], including new born [2].

• It is metabolised mainly by CYP3A4 and CYP2B6 [3]. CYP2B6 polymorphisms significantly influence the disposition of the drug and their prevalence is significantly higher in African population [4].

• The aim was to characterise the pharmacokinetics (PK) of nevirapine in African children and to identify patient characteristics influencing its disposition.

Methods

• Subjects - Combined data from following studies in African children:

Tab 1 Patient demographics:

<table>
<thead>
<tr>
<th>CHAPAS-1</th>
<th>CHAPAS-3</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>84</td>
<td>334</td>
</tr>
<tr>
<td>No of samples</td>
<td>547 (8)*</td>
<td>3004 (238)*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>6.16 [0.4 - 15]*</td>
<td>3.73 [0.44 - 12.3]*</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>15.11 [3.5 - 29]*</td>
<td>13.45 [5.5 - 30.0]*</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>iPk at week 6</td>
<td>SPK at week 6, 36, 60, 84, 108, 136*</td>
</tr>
<tr>
<td>Sampling scheme</td>
<td>0h, 1h, 2h, 4h, 6h, 8h, 12h</td>
<td>1-2 samples, 2-3h apart</td>
</tr>
<tr>
<td>Dosage</td>
<td>WHO 2006***</td>
<td>WHO 2010***</td>
</tr>
</tbody>
</table>

*Estimated from nonparametric bootstrap (n=50) of the final model, **Expressed as approximate %CV

• Samples excluded from analysis: unclear dosage history – 111, imputable (visual check confirmed by CWRES) – 87, BLQ confirmed by absence of the other drugs – 48.

• Model building - conducted using NONMEM 7.3 (FOCE-I) following an approach previously suggested to combine intensive and sparse data [5]; guided by differences in OFV, VPCs (generated in PSN) and other diagnostic plots (created in R). Stability of final model was validated by bootstrapping.

Results

Model structure is in Fig 1 and final parameters with results from bootstrap in Tab 3.

Figure 1 Structure of the final model.

• The data was best described using a 1-compartment model with absorption through 2 transit compartments [6] and first-order elimination.

• Allometric scaling was used to account for effect of size and was applied to CL and V [7]; typical values were estimated for a 14.5 kg child.

• The most significant determinant of nevirapine PK was a composite PGX SNP vector CYP2B6 516/S830 on CL [2]. Patients were allocated to 4 metaboliser groups based on their genotypes (Table 2).

Tab 2 Patient metabolic status

<table>
<thead>
<tr>
<th>Status</th>
<th>516GT</th>
<th>9830TC</th>
<th>Preval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast</td>
<td>GG</td>
<td>TT</td>
<td>33.1%</td>
</tr>
<tr>
<td>Inter</td>
<td>GG</td>
<td>TC</td>
<td>44.6%</td>
</tr>
<tr>
<td>Slow</td>
<td>TT</td>
<td>TC</td>
<td>21.7%</td>
</tr>
<tr>
<td>U-slow</td>
<td>GG</td>
<td>CC</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

• The model adequately describes the data. Uncertainty about the intake of the evening dose complicates the data of the observed lower trough concentrations in the evening than in the morning.

• Nevirapine metabolism in children is affected by a composite effect of 2 SNPs in CYP2B6: 516GT (rs3745274) and 9830TC (rs2839499).

• Based on differences in clearance, slow metabolisers should receive around 50% and ultra-slow (more rare) only 20% of the standard dose to maintain exposures comparable to the rest of the subjects.

• The lack of significance of a maturation effect could be due to small proportion of observations under 2 years of age.

Conclusions

• The model shows significant differences in clearance between the genotype sub-populations.

• Children with no available genotype information (n=79) were assigned to a group using a mixture model reflecting the prevalence in the rest of the cohort [8].

• Effect of age on CL (i.e. maturation) either expressed as a power function or sigmoidal function with Hill coefficient did not significantly improve model fit [7].

• Accounting for the effect of poor adherence and increased uncertainty about the time of unobserved doses preceding the sparse sampling by introducing a correction terms on RUV and BOV BIO improved fit.

References