Population Pharmacokinetics of Abacavir in Pregnant Women

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Running title: ABC Population pharmacokinetics
Abstract

For the first time, a population approach was used to describe abacavir pharmacokinetics in HIV infected pregnant and non-pregnant women. A total of 266 samples were obtained from 150 women. No covariate effect (age, bodyweight, pregnancy, gestational age) was found on abacavir pharmacokinetics. Thus, it seems not necessary to adapt ABC dosing regimen during pregnancy.

Short form Paper

Abacavir is a potent nucleoside reverse transcriptase inhibitor administered to treat human immunodeficiency virus (HIV) infection and prevent its transmission. Currently, regimens containing abacavir are still recommended as one of the first line options for adults including pregnant women (1). Abacavir pharmacokinetics has been previously investigated in adults (2–9) but only two limited studies (small number of patients, no once daily administration, narrow ranges of age and gestational age) were focused on pregnant women (10, 11). During pregnancy some physiological changes can affect the pharmacokinetics of a drug. Therefore, it is important to characterize these changes in a large population in order to use safely and efficiently the drug during pregnancy. Thus, ABC plasma concentrations in non-pregnant and pregnant women were analyzed using a population approach for the first time. The population pharmacokinetic parameters in HIV infected non-pregnant and pregnant women were estimated and the final model was used to determine if the current recommended doses produce efficient drug exposure in pregnancy.
The HIV-infected pregnant (n=36) and non-pregnant women (n=114) were (median [range]) 35.7 [15-67] years old and their body weight was 62.5 [40-102] kg. The gestational age at pharmacokinetic evaluation was 31 [9-41] weeks. A total of 266 samples were obtained from HIV infected women. Among these samples, 16 were collected in pairs (maternal and cord blood). Women received orally an ABC-containing regimen: 300 mg twice daily (47.9 %) or 600 mg once daily (52.1 %). Blood sampling were collected for therapeutic drug monitoring during a visit in the pharmacology unit of Hospital Cochin (Paris, France), therefore the times elapsed between drug administration and sampling times were variable. The pregnant women were enrolled at clinical sites of the ANRS-C01-French Perinatal Cohort (EPF). The mother of the child to be born provided signed informed consent. For the non-pregnant women, ethics committee approval and patient consent are not compulsory in France to use therapeutic drug monitoring data retrospectively. Plasma ABC concentrations were determined by high-performance liquid chromatography, as previously described (12). The limit of quantification (LOQ) was 0.02 mg/liter. Mean inter assay precisions of the lowest concentration of the quality controls was 10 %. The data were analyzed using NONMEM software (version 6.2) and the first order conditional estimation with interaction (FOCEI) method was applied (13). The 23 (8.6 %) concentrations below the LOQ (BLQ) were replaced by the LOQ/2 value (14). Use of the M3 method and the built-in M2 method were also tested for the BLQ data but they did not improve the results (15). A one compartment model with first order absorption and elimination was used to describe the data. The between-subject variability (BSV) could only be estimated for the apparent clearance. The combined model was not significantly better than the proportional model and the additive model was significantly worse than the combined model. Thus the
proportional error model was the best to describe the residual variability. The absorption constant (Ka) could not be well estimated, but the stability of the model was improved when the value was fixed to 1.8 h⁻¹, a value reported in adults by Jullien et al (4). No covariate (age, bodyweight, pregnancy, gestational age) had a significant effect on pharmacokinetics. So pregnant women and non-pregnant women had the same median population clearance. This is consistent with the previous studies reporting similar exposures between postpartum or non-pregnant women and pregnant women (10, 11). The final population pharmacokinetic estimates are summarized in Table 1.

The stability of the model and accuracy of the parameters were assessed by a bootstrap method implemented in Wings for Nonmem (WfN, http://wfn.sourceforge.net/). This method involves repeated random re-sampling with replacement from the original dataset for 1000 times. The parameters and their associated BSV were accurately estimated, and the confidence intervals (CIs) derived from the bootstrap analysis were reasonably narrow and did not include zero. The model was evaluated by the visual predictive check (VPC)(16) and the normalized prediction distribution errors (NPDE)(17). As confirmed by the VPC in Figure 1, the average prediction matched the observed concentrations and the variability was reasonably estimated. Moreover, the mean and the variance of the NPDE were not significantly different from 0 (p=0.10) and 1 (p=0.66) and the distribution was not different from normal one (p=0.53).

The placental transfer during pregnancy was estimated as the median fetal-to-maternal ratio concentrations at delivery. The median [min-max] estimated value was 104% [62%-163%]. This value is similar to those previously described [103%;106 %] (11, 12). We have tried to establish a model to describe fetal concentrations by connecting a
peripheral or an effect compartment. However, a successful convergence could not be obtained.

This study presents several limits. Pregnant and non–pregnant women could be included, allowing abacavir pharmacokinetics comparison between groups; however the number of pregnant women (n=36) was less important than the number of non-pregnant women (n = 114). Moreover this sparse sampling (1 or 2 samples per patient) could have led to a simplified model (one compartment model, fixed ka value) and these data from TDM resulted in a high residual variability. However the bootstraps, VPC and NPDE procedures gave a satisfactory evaluation the model.

To conclude, this is the first time that a population approach is used to describe abacavir pharmacokinetics in a large non-pregnant and pregnant women population. No covariate was found to influence abacavir pharmacokinetics, then pregnant and non-pregnant women had similar pharmacokinetics. Thus, it seems not necessary to adapt ABC dosing regimen during pregnancy.

References:


Legend:

**Figure 1:** Visual predictive check: comparison between the 5th (dashed line), 50th (full line) and 95th (dashed line) percentiles obtained from 1000 simulations and the ABC observed plasma concentrations (o) in pregnant women (A) and non-pregnant women (B). The model predictions and observations have been normalized to the median ABC dose, 600 mg.
Table 1: Population pharmacokinetics parameters of ABC from the final model

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Estimate</th>
<th>RSE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Ka$ (h$^{-1}$)</td>
<td>1.8*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CL/F (L.h$^{-1}$)</td>
<td>41.3</td>
<td>4.5</td>
<td>34.2-42.4</td>
</tr>
<tr>
<td>V/F (L)</td>
<td>119</td>
<td>5.8</td>
<td>91.9-123</td>
</tr>
<tr>
<td>$\omega_{CL/F}$</td>
<td>0.167</td>
<td>19.9</td>
<td>0.129-0.196</td>
</tr>
<tr>
<td>$\sigma_{ABC}$</td>
<td>0.438</td>
<td>13.6</td>
<td>0.434-0.574</td>
</tr>
</tbody>
</table>

RSE is the standard error of the estimate divided by the estimate and multiplied by 100. (95% CI are derived from a bootstrap procedure); * fixed value; $\omega$, square root of between-subject variance; $\sigma$, residual variability.