Timing of the postpartum curve in pharmacokinetic studies in pregnancy should not be too early

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• A European clinical pharmacology network to investigate the pharmacokinetics of newly developed antiretroviral agents in HIV-infected pregnant women

• Pregnancy may induce changes in PK of ARVs

• Possibly sub-therapeutic levels in pregnancy as a result
Outline PANNA study protocol

General study protocol, not specified per drug, 17 ARVs

PK curve 3rd trimester
Appr wk 33 gestational age

PK curve postpartum
at least 2 weeks after delivery
How does pregnancy affect pharmacokinetics?

- **Total body water**: increased
- **Plasma volume**: increased
- **Total body fat**: increased
- **Albumin conc.**: decreased
- **GFR**: increased
- **gastric pH**: increased
- **gastric emptying and intestinal motility**: decreased
- **CYP3A4 activity**: increased
- **CYP2D6 activity**: increased
- **CYP2C19 activity**: decreased

*Anderson, Clin Pharmacokinetics, 2005
Abduljalil, Clin Pharmacokin., 2012*
Physiological explanation

http://www.medicine.mcgill.ca/physio/vlab/other_exps/endo/reprod_horm.htm
Physiological explanation

Progesterone and estradiol cause

Inhibition of enzymes

Induction of enzymes

Induction of transporters – P-gp

Both AUC and $C_{\text{max}}$ can be affected
Research question

Post-partum curve is used as the control curve: normal, non-pregnant situation

Is this a valid assumption?

When should an increased dose in pregnancy be reduced?

PK curve at least 2 weeks after delivery
Methods

Compounds for which lower exposure in pregnancy was observed

AUC GMR (90% CI) third trimester/postpartum

- maraviroc (n=15)
- raltegravir (n=17)
- ritonavir (DRV QD)
- ritonavir (DRV BID)
- ritonavir (ATV)
- darunavir QD (n=9)
- darunavir BID (n=5)
- atazanavir (n=26)
- tenofovir (n=27)
- emtricitabine (n=24)
Methods

Normalise over different agents

Postpartum AUC and $C_{\text{max}}$ values were compared to accepted non-pregnant population AUC and $C_{\text{max}}$ for the specific agent

Ratio postpartum / population mean:

\[
\frac{\text{Individual postpartum AUC}}{\text{Population AUC for that compound/regimen}}
\]
Methods

The time-point of the postpartum curve was grouped per week. >8 weeks postpartum pooled

Kruskal Wallis test with weeks postpartum as grouping variable was used for statistical analysis.
Results

157 postpartum curves, from 67 unique patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at delivery (years)</td>
<td>32 (19-45)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>60%</td>
</tr>
<tr>
<td>White</td>
<td>39%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
<tr>
<td>Weight at postpartum (kg)</td>
<td>71 (43-126)</td>
</tr>
<tr>
<td>Weight at 3(^{rd}) trimester (kg)</td>
<td>76 (48-139)</td>
</tr>
</tbody>
</table>
Results

Number of curves

Weeks postpartum

Number of curves

- NRTI
- PI
- II
- EI
Results

AUC relative to reference

Kruskall Wallis
p = 0.337
Results

$C_{\text{max}}$ relative to reference

Kruskall Wallis

$p = 0.227$
Conclusion

- No time effect was observed for postpartum curves taken at least 3 weeks post delivery

- Postpartum curves from at least 3 weeks post delivery were comparable to non-pregnant population means

- Dose reductions (after dose increase in pregnancy) should be considered from > 2 weeks post delivery onwards
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Investigators of the PANNA study

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Website: panna
www.pannastudy.com