Substantially Lower Rilpivirine Plasma Concentrations during Pregnancy

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Abstract # 754

BACKGROUND

- It is important to achieve effective blood concentrations of antiretroviral drugs to prevent treatment failure and the development of resistance. The physiological changes during pregnancy influence the pharmacokinetics of drugs. In most cases this process results in a decreased exposure during pregnancy. Limited data are available on rilpivirine pharmacokinetics during pregnancy and on the placental passage of rilpivirine. Another study by the IMPACT group reported that rilpivirine exposure was lower during pregnancy compared with postpartum and highly variable. Ninety percent of women had minimum concentrations above the protein binding-adjusted EC90 for rilpivirine (0.012 mg/L).

- In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA).

OBJECTIVES

1. Here we present preliminary data on trimester exposure to rilpivirine and cord blood concentrations at delivery.
2. To describe the safety of the antiretroviral agents during pregnancy and monitor viral load response and pregnancy outcomes.

METHODS

- Data presented were collected in the PANNA study; “Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women” (Ewomen) (ClinicalTrials.gov identifier NCT010829529).
- Non-randomised, open-label, parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits patients from HIV treatment centers in Europe.
- Here, we report on pregnant HIV-infected patients treated with rilpivirine 25 mg once daily as part of their ART.

RESULTS

- Blood was collected for 24-hour pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24) after observation of intake of the medication in the third trimester. After at least 2 weeks continuation of therapy post-partum, intensive PK sampling was repeated. Where possible a cord blood sample and matching maternal blood sample was taken at delivery to estimate placental transfer.
- Safety and attrition parameters were evaluated.
- Total rilpivirine plasma concentrations were determined with a validated UPLC method and an LLOQ of 0.0063 mg/L.
- Pharmacokinetic parameters were calculated using Phoenix (Certara) version 6.3. Bioequivalence analysis was conducted using Phoenix.

RESULTS (continued)

- Two out of 16 patients had a sub-therapeutic C0 (< 0.04 mg/L) in the third trimester (0.039 mg/L, and 0.035 mg/L respectively), no sub-therapeutic levels were observed postpartum.
- The median (range, n=5) ratio of cord blood/maternal plasma RPP concentrations was 0.5 (0.36-0.91).

Table 1: Subject characteristics and pregnancy outcomes

| Age (years) | 28 (10-38) |
| Weight (kg) | 81 (44-122) |
| BMI (kg/m²) | 28 (21-35) |
| Gestational age (weeks) | 30 (25-32) |
| Trimester and treatment arm | 25% (Q1-Q3) | 25% (Q1-Q3) | 25% (Q1-Q3) |
| LLOQ (mg/L) | 0.0063 (0.0063) |
| ULOQ (mg/L) | 10 mg/L |
| Tmax (h) | Median 4 (IQR 2-6) |
| T1/2 (h) | Median 18 (IQR 12-25) |
| VD (L) | 0.002 (6.3-4.1) |
| Cmax (mg/L) | Median 25 (IQR 11-35) |

Table 2: Total RPP 25 mg QD geometric mean (% C0) pharmacokinetic parameters in third trimester and postpartum and geometric mean ratios (90% CI)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Third Trimester</th>
<th>Postpartum</th>
<th>GM Ratio (% C0)</th>
<th>Third trimester postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUCt(0-24) [h mg/L]</td>
<td>1.73 (0.77-3.93)</td>
<td>0.77 (0.40-1.52)</td>
<td>88 (68-114)</td>
<td>2.18 (1.30-3.63)</td>
</tr>
<tr>
<td>C0 (mg/L)</td>
<td>0.11 (0.04-0.26)</td>
<td>0.17 (0.07-0.39)</td>
<td>155 (78-315)</td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>0.06 (0.02-0.15)</td>
<td>0.13 (0.07-0.24)</td>
<td>22 (14-36)</td>
<td></td>
</tr>
<tr>
<td>Css (mg/L)</td>
<td>0.05 (0.02-0.10)</td>
<td>0.10 (0.05-0.20)</td>
<td>21 (10-45)</td>
<td></td>
</tr>
<tr>
<td>C0/CSS</td>
<td>1.60 (0.98-2.84)</td>
<td>1.10 (0.64-1.98)</td>
<td>146 (60-336)</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetics (continued)

- Mean concentration-time profiles of RPP 25 mg QD during third trimester and postpartum are shown in Figure 1. The reference concentration-time profile is based on the study from Lamorde, 2015, including 15 patients using 25 mg RPP.
- GM pharmacokinetic parameters of RPP 25 mg QD in trimester and postpartum are shown in Table 2.
- GM ratios and 90% confidence intervals (90% CI) of pharmacokinetic parameters of RPP 25 mg QD in trimester compared to postpartum are shown in Table 2.
- Individual pharmacokinetic parameters after RPP 25 mg postpartum are shown in Figure 2.

CONCLUSIONS

- Sixteen HIV-infected pregnant women were included in this analysis.
- Subject characteristics per trimester and pregnancy outcomes are shown in Table 1.

- Mean concentration-time profiles of RPP 25 mg QD during trimester and postpartum are shown in Figure 1. The reference concentration-time profile is based on the study from Lamorde, 2015, including 15 patients using 25 mg RPP.
- GM pharmacokinetic parameters of RPP 25 mg QD in trimester and postpartum are shown in Table 2.
- GM ratios and 90% confidence intervals (90% CI) of pharmacokinetic parameters of RPP 25 mg QD in trimester compared to postpartum are shown in Table 2.
- Individual pharmacokinetic parameters after RPP 25 mg postpartum are shown in Figure 2.

Figure 1: Mean (±SEV) concentration-time profile after administration of RPP 25 mg QD during third trimester and postpartum

Figure 2: RPP 25 mg QD individual pharmacokinetic parameters during third trimester and postpartum

Safet

- One SAE was reported: admission to the hospital because of irregular contractions, the SAE was judged not to be related to rilpivirine. In total 13 adverse events were reported by 8 patients. None were judged to be related to rilpivirine.
- No children were HIV-infected, no birth defects were reported. No major safety concerns were observed.
- No preterm births were observed, one baby with low body weight (<2500 g) at birth and three (19%) children small for gestational age.

CONCLUSIONS

- In this study exposure to RPP was about 50% lower in the third trimester of pregnancy, however, in this limited number of patients, this did not lead to detectable maternal viral load.
- It is important that RPP is taken with a meal during pregnancy and we would advise TDM in the third trimester to avoid sub-therapeutic exposure.

Acknowledgements

The second trimester cohort of 75 pregnant women from 12 centers participated in the protocol and the staff of the participating centers. The PANNA network is supported by the Dutch Ministry of Health, Welfare and Sport, the Flemish Ministry of Health and the Provinces of Flanders and Zeeland, and Stichting Prevention en Zorgaangaanwezigheid in Haastrecht.