PHARMACOKINETICS OF NEVIRAPINE PROPHYLAXIS IN HIV-EXPOSED LOW BIRTH WEIGHT INFANTS

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Introduction

- HIV-infected women are at high risk of delivering low birth weight (LBW) and premature (< 37 weeks gestation) infants1
- HIV-exposed LBW infants, < 2500 grams, require access to antiretroviral (ARV) post exposure prophylaxis
- Adequate pharmacokinetic (PK) data are available only for zidovudine in LBW infants2
- There are few PK and safety data for nevirapine (NVP) in LBW infants3, who undergo developmental changes that influence PK4

Objective

- To describe the PK and safety of NVP in HIV-exposed LBW infants receiving NVP prophylaxis as part of routine care from birth to 24 weeks of life
- IMPAACT P1106 is a Phase IV study of the PK and safety in LBW infants receiving ARVs and tuberculosis medicines in their clinical care.
- Sites: Family Clinical Research Unit (FAM-CRU) in Cape Town and the Perinatal HIV Research Unit (PHRU) in Johannesburg, South Africa
- This study consists of six arms, of which arm 1 focused on NVP for prophylaxis of peripartum and breast milk mother-to-child transmission.
- Infants were stratified by birth weight: - <1400 g - 1400 g – <1800 g - 1800 g – <2500g
- NVP was dosed at 2 mg/kg once daily (birth to 14 days of age), followed by 4 mg/kg once daily
- Infant characteristics, PK samples and safety data were collected at study entry (week 1; day 7-14 of age) and at 4, 6, 10, 16 and 24 weeks of age.
- Plasma samples for NVP assay were collected pre-dose and 2 hours post dose at study entry and pre-dose at all other study visits
- Plasma samples were assayed for NVP by using liquid chromatography–mass spectrometry (lower limit of detection of 0.02 µg/ml)
- The NVP trough target was > 0.1 µg/ml. NVP trough concentrations were normalized to a 2 mg/kg dose for analysis
- Adverse events (AEs), potentially harmful to an infant, were classified as follows:
  * Expected: events pre-identified as commonly associated with prematurity
  * Unexpected: unanticipated events not commonly associated with prematurity

Methods

- In August 2016, 94 NVP trough concentrations were available for 27 infants.
- Table 1. Baseline characteristics of LBW infants on NVP (n=40)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male gender (n, %)</th>
<th>Ethnicity (Black African) *(n, %)</th>
<th>Birth weight, g (mean, range)</th>
<th>Gestational age, weeks (mean, range)</th>
<th>Enrolment age, days (mean, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 (45)</td>
<td>38 (95)</td>
<td>1675 (890 – 2460)</td>
<td>33 (28-40)</td>
<td>11 (8-14)</td>
</tr>
</tbody>
</table>
  *2 infants were of mixed race

- Table 2. Characteristics of LBW infants on NVP at time of PK sampling (n=27)
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean and (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td>1383 (950-2390)</td>
</tr>
<tr>
<td>Current weight, g</td>
<td>2147 (965-6050)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>31 (28-38)</td>
</tr>
<tr>
<td>Postmenstrual age, weeks</td>
<td>37 (29-56)</td>
</tr>
<tr>
<td>NVP dose, mg/kg</td>
<td>3.4 (1.38-3.7)</td>
</tr>
</tbody>
</table>

- Figure 1. 94 NVP trough concentrations across study visits from day 7 to week 24.
- Figure 2. Observed NVP trough concentrations versus gestational age at initial visit (n=26)
- Figure 3. Observed NVP concentrations versus postnatal age in days over study period (n=94)

- MPH was administered for a mean duration of 10 weeks (range of 1.5 – 18.8 weeks).
- The mean NVP trough concentration across all visits was 1.87 µg/mL (range < 0.02 - 10.69 µg/mL); 6/9 (6%) observations were < 0.1 µg/mL (NVP prophylaxis target)
- Below target samples were all from later visits (median postmenstrual age 44 weeks; median weight of 3903g) when at home and receiving NVP from caregiver.

Results

- NVP was administered for a mean duration of 10 weeks and May 2016
  - <1400 g: n = 12
  - 1400 – <1800 g: n = 12
  - 1800 – 2500g: n = 16

- Table 1. Baseline characteristics of LBW infants on NVP (n=40)

- Table 2. Characteristics of LBW infants on NVP at time of PK sampling (n=27)

- At the initial visit, lower gestational age was associated with higher NVP trough concentration normalized for dose (r = -0.47; p<0.02)

- Figure 3. Observed NVP concentrations versus postnatal age in days over study period (n=94)

- Across all visits, NVP trough concentrations normalized for dose were inversely related to infant postnatal age (r = - 0.45, p<0.001)

- The NVP dosing regimen achieved trough concentrations above the 0.1 µg/mL prophylaxis target
- NVP trough concentration at the initial visit increased with decreasing gestational age
- Subsequent NVP concentrations decreased with increasing postnatal age
- No treatment related adverse events were observed

Conclusions

- The NVP dosing regimen achieved trough concentrations above the 0.1 µg/mL prophylaxis target
- NVP trough concentration at the initial visit increased with decreasing gestational age
- Subsequent NVP concentrations decreased with increasing postnatal age
- No treatment related adverse events were observed

Safety results

- All AEs were unrelated to NVP
- Three infants died during the study period:
  - 2 sudden unexpected death in infancy (SUDI) at 7 and 17 weeks of age
  - 1 Acinetobacter baumanii sepsis at 4 weeks of age
- 10 had Grade 3/4 unexpected AEs, most common being pneumonia (n=4)
- 9 infants had Grade 3/4 expected AEs that commonly occur in premature infants, the most frequent being presumed or confirmed sepsis (n=6)
- The majority of grade 3/4 AEs resolved or were downgraded to a Grade 1/2 by study end

References

4. Kearns GL, Abdelbaum LG, Perinatal HIV Research Unit, University of Witwatersrand, Johannesburg, South Africa, 17 weeks of age
5. At time of enrolment, lower gestational age was associated with higher NVP trough concentration normalized for dose (r = -0.47; p<0.02)

Acknowledgements

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