Therapeutic NVP Dosing in Infants

Brookie M. Best, PharmD, MAS
Infant NVP Considerations

- Very early antiretroviral treatment (ART) initiation in HIV infected newborns may limit the seeding of viral reservoirs and maintain immune responses.
- NVP safety and dosing are well established for prophylactic doses (2mg/kg) but this dose does not achieve therapeutic NVP concentrations (> 3 mcg/mL).
- Higher NVP doses are needed for newborn treatment.
Nevirapine PK Issues

- NVP induces its own metabolism
- Consistent and extensive absorption from gut
- Lead-in dosing impact on troughs compounded in infants with shorter half-life
- Developmental changes in NVP metabolism
  - Newborns with immature metabolism
  - Older infants have increased metabolism
  - Prematurity associated with reduced metabolism
- Higher CL/F and shorter $t_{1/2}$ in older infants and young children
- Polymorphism in CYP2B6 (516TT) associated with lower NVP CL and higher levels
Nevirapine Pharmacodynamics

- Target NVP trough for prophylaxis is 100 ng/mL (0.1mcg/mL) based on IC50.
- NVP treatment troughs < 3 mcg/mL associated with clinical failures (de Vries Sluijs et al Clin PK 2003).
- Rash seen in 47% of adults in Phase I study with 400mg qd - rationale for lead-in & bid dosing.
- In African women Gr3+ rash is associated with higher NVP troughs (8.7 vs. 7.2 mcg/mL) (Dong et al AIDS 2012).
- 12 hydroxy-metabolite may be responsible for hepatotoxicity.
- Most studies show no association between NVP levels and liver toxicity in patients without hepatitis.
Pop PK Model of NVP in Infants

Impact of Factors Influencing NVP PK

- Term First-Dose
- Term Multi-Dose
- Poor Metabolizer CYP2B6
- Prematurity GA 34 Week
- Adult Multi-Dose

Mirochnick et al. CROI 2016
Predicted NVP Levels in Infants with 6 mg/kg Based on PopPK Model – Mirochnick et al CROI 2016
NVP in Early HIV Treatment Studies

- Retrospective – Lau et al 150mg/m^2 with lead-in
- The Early Infant Treatment Study in Botsawna (BHP 074 R. Shapiro et al) – 6mg/kg bid:
  - NVP PK results after 1 and 2 weeks of treatment on first 6 subjects presented at CROI 2016 (Capparelli Abs#815)
  - NVP PK at Weeks 1 and 2 looked similar
    - median trough 3.6 mcg/mL all < 11 mcg/mL
- P1115 - Very Early Intensive Treatment of HIV-Infected Infants to Achieve HIV REMISSION: A Phase I/II Proof of Concept Study (Y Bryson / E Chadwick et al) – Term (GA ≥ 37 wk) 6mg/kg bid / (GA 34-<37 wk) 4mg/kg bid
NVP PK in Newborns Receiving Treatment Dosing – Lau et al

- Retrospective study of 22 infants – median GA 37 weeks; BWT 2.9 kg.
- Initial NVP dose 150 mg/m² (~10 mg/kg) bid with 14 day qd lead-in.
- TDM applied to achieve NVP 3-8 mg/mL.
- Median (range) NVP troughs:
  - Week 1 – 9.2 (1.6 – 25.4)
  - Week 2 – 4.1 (1.6 – 26.1)
  - Week 4 – 3.8 (0.2 – 17.1)
BHP 074 PK Results and Conclusions

**Pharmacokinetic (PK) evaluations performed in the first 6 infants**

**PK samples at 1 and 2 weeks of treatment analyzed**

**Subject Characteristics**
- Median GA at birth: 37.0 ± 1.9 weeks
- Median age at start of ART: 2.8 ± 1.7 days

**No drug toxicities identified**

**Median NVP trough concentration = 3.6 mcg/mL**

**Conclusions**
- Values consistent with typical adult NVP concentrations
- This dosage worthy of further study to determine safety and activity
P1115 PK Elements

- **2 Cohorts**
  - Cohort 1: High Risk
  - Cohort 2: HIV Infected
- **Dose**
  - $\geq 37$ wk GA: 6mg/kg bid
  - 34-<37 GA: 4mg/kg bid
- Sparse Plasma and DBS collected at WK 1 & 2 in first 30 Cohort 1 participants.
- DBS collected at regular intervals while receiving NVP.
- Target NVP 3-10 mcg/mL.
- Goal: <20% above and <20% below NVP target. (within subject mean).
Stay Tuned

• P1115 initial NVP results to be presented at IAS, summer 2016.