Nevirapine Pharmacokinetics in HIV-exposed Neonates Receiving Triple Combination Antiretroviral Therapy as Post-Exposure Prophylaxis

Lau E, Brophy J, Samson L, Campbell D, Yudin M, Murphy KE, Seto W, Colantonio D, Read S, Bitnun A.

6th International Workshop on HIV Pediatrics
July 18-19, 2014, Melbourne, Australia

Study team

Principal investigator

- Ari Bitnun[1] MD, MSc, FRCPC

Co-investigators

- Elaine Lau[2] BScPhm, PharmD, MSc, ACPR, RPh
- Jason Brophy[3] MD, MSc, FRCPC
- Lindy Samson[3] MD, FRCPC
- Douglas Campbell[4] MD, FRCPC
- Mark Yudin[5] MD, MSc, FRCSC
- Kellie E. Murphy[6] MD, MSc, FRCSC
- Winnie Seto[2] BScPhm, PharmD, MSc, ACPR, RPh
- David Colantonio[7] PhD, DABCC
- Stanley Read[1] MD, PhD, FAAP, FRCPC

[1]Hospital for Sick Children, Infectious Diseases, Toronto, Canada
[2]Hospital for Sick Children, Pharmacy, Toronto, Canada
[3]Children's Hospital of Eastern Ontario, Infectious Diseases, Ottawa, Canada
[4]St. Michael's Hospital, Pediatrics, Toronto, Canada
[5]St. Michael's Hospital, Obstetrics and Gynecology, Toronto, Canada
[6]Mount Sinai Hospital, Maternal Fetal Medicine, Toronto, Canada
[7]Hospital for Sick Children, Paediatric Laboratory Medicine, Toronto, Canada

Disclosures

- No conflicts of interest to declare

Background

- Neonates at high-risk of HIV infection receive triple combination antiretroviral therapy (cART) with AZT/3TC/NVP for post-exposure prophylaxis at our institutions
- NVP dose extrapolated from treatment dose in older infants and children, aiming for therapeutic rather than prophylactic drug levels
- NVP dose for PEP in neonates requires validation
  - Neonates may require a different dose than older infants due to differences in age-related drug clearance
  - Possible association between higher NVP levels and toxicity (rash, transaminitis)
  - No studies to date evaluating pharmacokinetics and safety of therapeutic NVP doses in pre-term infants or infants <2 weeks postnatal age

Study Objectives

- Primary objectives
  - To evaluate whether the current nevirapine dose for HIV PEP achieves therapeutic drug levels in newborn infants at high risk of HIV infection using therapeutic drug monitoring (TDM)
  - To evaluate the pharmacokinetics and safety of the nevirapine PEP dose
- Secondary objectives
  - To explore patient factors associated with differences in nevirapine drug disposition

Methods

- Study Design
  - Multicenter, prospective, observational pharmacokinetic study
- Patient Population
  - Newborn infants prescribed NVP-based cART for HIV-PEP between April 2012- January 2014
  - Exclusion
    - <32 weeks gestational age
    - Life-threatening medical conditions
    - Unable to take oral medications
    - Mothers have nevirapine-resistant virus

Methods (cont'd)

- Drug administration and sampling
  - Empiric NVP dose
    - 150 mg/m^2 orally once daily for 14 days, then 150 mg/m^2 orally every 12 hours for 14 days (total 4 weeks)
  - Concomitant ARVs (as per DHHS guidelines):
    - AZT/3TC x 6 weeks
  - Therapeutic Drug Monitoring
    - Timing of NVP levels
      - Weeks 1 and 2: pre-dose (trough)
      - Week 4: pre-dose (trough), 1 and 4 hours post-dose
    - Target range: 3-8 mg/L
      - Usual *prophylaxis* target is >0.1 mg/L (10 times the in vitro IC_{50} of NVP against wild-type HIV-1)
    - Dose adjustment at weeks 1 & 2 if NVP levels fell >20% outside target range

Data Collection

- Chart review for maternal antenatal information and clinical characteristics of infants (demographics, growth parameters, concomitant medications)
- Caregiver interviews for medication adherence and self-report of NVP-related adverse events
- Laboratory monitoring
  - CBC (with differential), AST, ALT, bilirubin, alkaline phosphatase, lactate, and serum creatinine, at baseline, 2 and 4 weeks
  - HIV DNA PCR – within 48 hours of birth, 4 weeks (±1 week) of age, 8 weeks (±2 weeks) of age and 4 to 6 months of age

Data Analysis

- Descriptive statistics
  - Infant and maternal characteristics
  - Proportion of NVP levels within therapeutic range
  - Number and types of adverse effects

- Univariate analysis
  - One-way ANOVA – factors related to NVP disposition

- Pharmacokinetic analysis
  - PK parameters calculated using non-compartmental model
    - *Oral clearance (CLssF)(L/kg/hr)*
    - *Area under the Curve over dosing interval (AUC_τ)(mg/L*hr)*

Results

- 22 newborn infants with at least one nevirapine trough level
- 12/22 infants had trough and post-levels available for more complete pharmacokinetic analysis

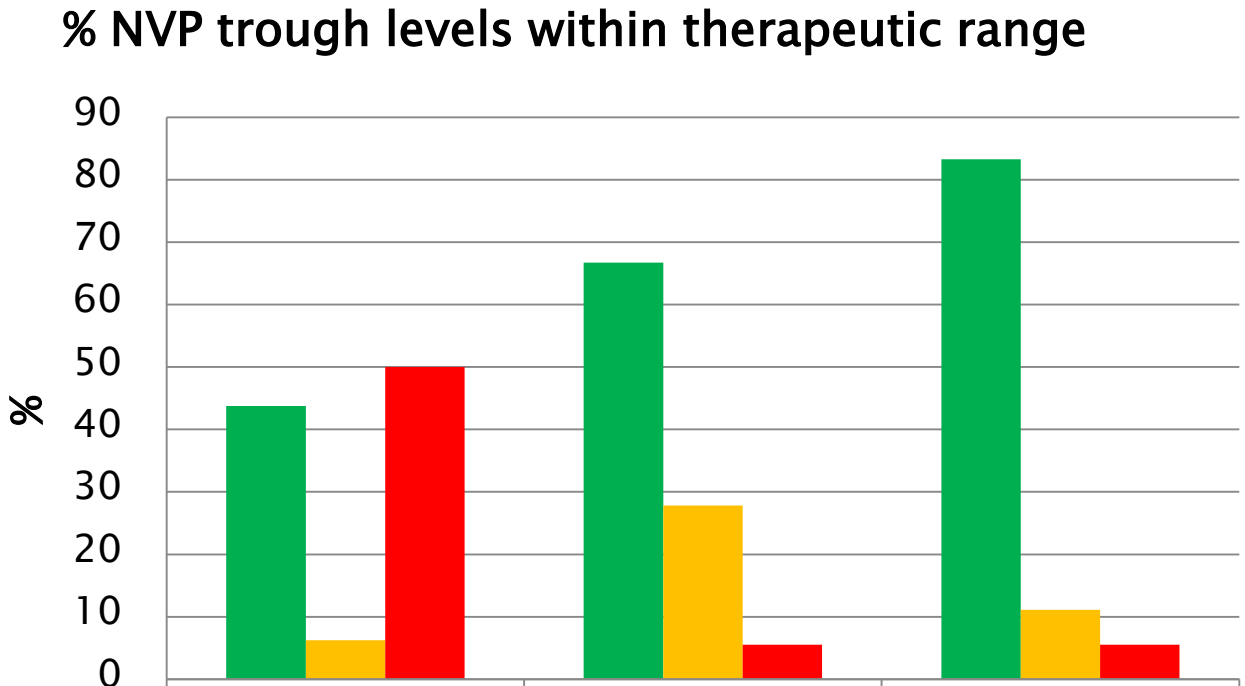
Patient characteristics	No. (%)
Gestational age (weeks), median (range)	37.2 (30.0 – 41.7)
Premature (<37 weeks gestation)	4 (18.2%)
Birth weight (kg), median (range)	2.91 (1.05 – 3.61)
Gender; male	13 (59.1%)
Ethnicity: • African/Black • Caucasian • Asian • Aboriginal • Unknown	 13 (59.1%) 6 (27.3%) 1 (4.5%) 1 (4.5%) 1 (4.5%)
Reason for cART PEP • HIV+ mother, uncontrolled VL • Mother deemed high risk of HIV infection	 12 (54.5%) 10 (45.5%)

Nevirapine Pharmacokinetics

Nevirapine Trough Levels

	Median	Range
Week 1	9.2 mg/L	1.6 – 25.4
Week 2	4.1 mg/L	1.6 – 26.1
Week 4	3.8 mg/L	0.2 – 17.1

Nevirapine Pharmacokinetics



	Week 1 (n=16)	Week 2 (n=18)*	Week 4 (n=18)*
Therapeutic	43,75	66,7	83,3
Subtherapeutic	6,25	27,8	11,1
Supra-therapeutic	50	5,5	5,5

*3 cases required dose adjustment at week 1, and 3 cases required dose adjustment at week 2

Nevirapine Pharmacokinetics

Factors affecting drug clearance

	N	Mean CLss_F (L/kg/hr)	SD	p-value
Race				
Caucasian	5	2.99	2.61	0.760
African/Black	13	4.62	4.63	
Other	2	3.66	4.61	
Total	20	4.11	4.08	
Gender				
Male	12	3.68	4.37	0.500
Female	9	4.91	3.56	
Total	21	4.20	3.99	
Birth weight (kg)				
<1.5	1	0.39	n/a	0.325
1.5-2.5	3	1.89	2.32	
>2.5	17	4.84	4.12	
Total	21	4.20	3.99	
Gestational Age (weeks)				
≤ 32	4	1.51	2.04	0.294
>32 - 37	1	1.79	n/a	
>37	15	4.90	4.29	
Total	20	4.07	4.05	

Nevirapine Pharmacokinetics

Factors affecting drug exposure

	N	Mean AUCτ (mg/L*hr)	SD	p-value
Race				
Caucasian	5	19.1	15.5	0.721
African/Black	13	15.7	18.7	
Other	2	27.3	32.4	
Total	20	17.7	18.5	
Gender				
Male	12	22.1	22.2	0.152
Female	9	10.4	8.3	
Total	21	17.1	18.2	
Birth weight (kg)				
<1.5	1	38.5	n/a	0.196
1.5-2.5	3	29.2	22.6	
>2.5	17	13.6	16.8	
Total	21	17.1	18.3	
Gestational Age (weeks)				
≤ 32	4	31.6	19.1	0.253
>32 - 37	1	16.8	n/a	
>37	15	14.1	17.7	
Total	20	17.7	18.5	

Safety

Types of adverse events (from all causes)

Adverse event (n = 59)	No. (%)
Clinical	
Neurologic (tremors, irritability)	8 (13.6)
GI (spitting up/vomiting, diarrhea, gas)	8 (13.6)
Respiratory (respiratory distress, SOB)	3 (5.1)
Laboratory abnormalities	
Anemia (Hb < 115 g/L)	11 (18.6)
Neutropenia (ANC < 1.5 x 10^9/L)	12 (20.3)
Hyperlactatemia (lactate >2.4 mmol/L)	14 (23.7)
Increased serum creatinine (>56 μmol/L)	1 (1.7)
Hyperbilirubinemia (unconj bili (>70 μmol/L)	3 (5.1)

Safety

- Adverse event severity
  - Grade 1 – 67.8%
  - Grade 2 – 23.7%
  - Grade 3 – 5.1%
  - Grade 4 – 1.6%
- No cases of rash, transaminitis, or hepatotoxicity
- Treatment discontinuation not required for any adverse event

HIV Transmission

- No cases of HIV transmission were documented

Discussion

- High proportion (50%) of NVP levels exceeded target range in the first week, but majority of levels within target by week 4
- NVP levels decreased over time with empiric dosing, even without further dose adjustments
  - Drug clearance likely increases over time with maturity and induction of CYP P450 metabolizing enzymes (increased metabolism)
- Some patients had sub-therapeutic levels, but exceeded prophylaxis target of >0.1 mg/L in all cases and no cases of vertical transmission
  - In previous studies, alternate NVP extended-dosing PEP regimens failed to maintain prophylactic targets beyond day 10 of life

Mirochnick et al. JAIDS 2008;47:334-337)

Discussion

- High interpatient variability in PK parameters due to small sample size
- Association between lower birth weight and reduced drug clearance/increased drug exposure consistent with previous studies *(*
  - Further research needed to determine effects of other predictors (e.g. CYP2B6 genetic polymorphism)
- Nevirapine well-tolerated at therapeutic doses for PEP in neonates
  - Laboratory abnormalities attributable to AZT/3TC (anemia, neutropenia) or physiologic findings in neonates (hyperbilirubinemia)
  - Unable to test for association between NVP levels and adverse effects, given small number of adverse effects clinically attributed to NVP

Mugabo et al. S Afr Med J. 2011;101:655-658

Conclusions

- Generally, we found that our current dosing strategy achieved therapeutic levels for most patients after 1 week

- For nevirapine PEP in low birth weight and/or premature infants, lower empiric dosing given less frequently and/or close monitoring with TDM and dose adjustment as needed, may be required

Acknowledgements

- This work was supported by a grant provided by the Canadian Foundation for AIDS Research (CANFAR)

- We wish to thank the many families who agreed to participate in this study