NEVIRAPINE DOSING FOR TREATMENT IN THE FIRST MONTH OF LIFE

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Abstract

Background: NVP clearance (CL) is low in term neonates and further decreased in premature infants due to immaturity in CYP2B6 and CYP3A4 activity. NVP autoinduces its own CL but the extent of autoinduction on immature enzyme systems is unknown. While pharmacokinetic (pk) studies have been done to determine NVP dosing regimens for treatment of HIV infection (trough conc target 3.0 ug/mL) in infants after 1 month of life, NVP pk studies under age 1 month have been limited to evaluations of dosing regimens for prophylaxis against HIV infection (trough conc target 0.1 ug/mL). Population modeling of these pk data and simulations can be used to evaluate proposed NVP dosing regimens to meet treatment target conc in term and late preterm infants (34-37 weeks gestation) from birth through 6 months of life.

Methods: We developed a NVP population pk model using NONMEM that incorporated data for 192 infants (1121 plasma NVP conc) from US, Africa and Brazil under age 1 yr in 5 PACTG or HPTN protocols. Dosing regimens from birth through 6 months of age were evaluated using simulations. Simulated NVP doses included 6 mg/kg BID for term infants and 4mg/kg BID for 1 week followed by 6 mg/kg BID for late preterm infants. Proposed PK target was NVP trough conc > 3.0 ug/mL.

Results: A one compartment model with first order absorption was used. CL was scaled allometrically and volume of distribution (Vd) was scaled linearly for weight. CL was modeled to mature exponentially with age. Autoinduction of CL was modeled as a linear function of dose. The effects of prematurity and maturation of CYP2B6 and CYP3A4 activity on NVP CL were imputed from published studies. Typical CL (L/hr/kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and by an additional 79% due to induction. Final simulations used term infant doses of 6 mg/kg BID and late preterm infant doses of 4mg/kg BID for 1 week followed by 6 mg/kg BID. In these simulations, the dosing regimens achieved the NVP trough target.

Conclusions: NVP CL is low immediately after birth and increases dramatically over the 1st months of life. Appropriate NVP dosing regimens in neonates must take into account the impact of maturation, autoinduction and prematurity on NVP CL. The dosing regimens supported by these simulations and NVP PK in preterm infants are being studied in the IMPAACT 1115 and 1106 protocols.

Introduction

Nevirapine (NVP) is eliminated primarily via hepatic metabolism by the cytochrome P450 enzymes 2B6 and 3A4, followed by renal excretion. NVP clearance is low in term neonates and further decreased in premature infants due to immaturity in CYP2B6 and CYP3A4 activity. In addition, in adults and older children receiving chronic therapy with NVP there is autoinduction of the metabolic pathway, so that after 2 weeks of treament NVP clearance increases 1.5 to 2 fold and mean elimination half life falls by 50%.

PK studies of NVP in neonates were designed to support its use in prevention of HIV transmission from mother to child. The goal of these studies was to define neonatal NVP dosing regimens that would maintain NVP trough concentrations above 0.1 ug/mL.

Recent trends to early diagnosis of HIV infected neonates and provision of fully suppressive antiretroviral regimens to such infants have led to interest in use of NVP as part of early treatment regimens for neonates. The standard trough concentration target for NVP used for treatment of HIV infection is 3.0 ug/mL. While PK studies have been done to determined NVP doses to meet this treatment target in infants over 1 month of age, no PK studies have been done to establish doses to meet this treatment target in neonates during the first month of life.

Objective

- To use population modeling of existing neonatal and infant NVP pk data and simulations to evaluate proposed NVP dosing regimens to meet treatment target concentrations in term and late preterm infants (34-37 weeks gestation) from birth through 6 months of life.

Study Methods

- Subjects were infants under 1 year of age enrolled in one of 5 protocols:
  1. PACTG 250 – phase I study of NVP safety and pharmacokinetics after single maternal intrapartum and infant postpartum doses in US[1,2]
  2. HIVNET 006 - phase I study of NVP safety and pharmacokinetics after single maternal intrapartum and infant postpartum doses in Uganda[3]
  3. PACTG 356 – phase I/II study of safety and pharmacokinetics of early intensive combination antiretroviral therapy in HIV infected infants[4]
  4. HIVNET 023 – phase I/II study of the safety and pharmacokinetics of NVP given as prophylaxis in breast feeding infants during the first 6 months of life[5]
  5. HPTN 040 - phase III randomized trial of the safety and efficacy of 3 neonatal antiretroviral regimens for prevention of intrapartum HIV-1 transmission
- Database including subject demographic and clinical characteristics, dosing, sampling times and NVP concentrations was compiled.
- NONMEM used to model changes in NVP pharmacokinetic parameters over time.
- Graphical and statistical analyses used to evaluate model fit.
- CYP2B6 metabolizer status, rate of autoinduction, and prematurity effects imputed from literature.
- Simulations were used to evaluate proposed regimen of 6 mg/kg BID for term infants and 4mg/kg BID for 1 week followed by 6 mg/kg BID for late preterm infants. Target was to achieve NVP trough conc > 3.0 ug/mL.

Dosing and Sampling Regimens

1. PACTG 250 – Intensive sampling - first week of life
   a. 10 newborns – intrapartum maternal dosing only (100 or 200 mg)
   b. 8 newborns – 200 mg maternal intrapartum dosing, single 2 mg/kg infant dose at 48-72 hours
   c. 10 newborns – prenatal maternal dosing for up to 14 days, 200 mg maternal intrapartum and infant postnatal 2 mg/kg dosing
2. HIVNET 006 – Intensive sampling – first week of life
   a. 8 newborns – intrapartum maternal dosing only (200 mg)
   b. 8 newborns – 200 mg maternal intrapartum dosing, single 2 mg/kg infant dose at 48-72 hours
3. PACTG 356 – Sparse sampling – 1 month – 1 year old
   a. 46 HIV infected infants between 1 month -1 year of age received 120 mg/m2 q day for 14 days, then 200 mg/m2 q12h
4. HIVNET 023 – Sparse sampling at 2, 8, 16 20 and 24 weeks
   a. 58 infants received daily, twice weekly or weekly dosing (2 or 4 mg/kg x14 days, then 4 or 8 mg/kg) from birth through age 6 months
5. HPTN 040 – Intensive sampling (14 infants), Sparse sampling (30 infants) – first 2 weeks of life
   a. 44 newborns – no maternal dosing, infant doses within 48 hours of birth, 48 hours after the first dose and 96 hours after second dose

Results

- One compartment model with first order absorption
- CL scaled allometrically and volume of distribution (Vd) scaled linearly for weight
- CL modeled to mature exponentially with age.
- Autoinduction of CL was modeled as a linear function of dose.
- The effects of prematurity, CBY2B6 polymorphism and rate of autoinduction on NVP CL were imputed from published studies.
- Typical CL (L/hr/kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and autoinduction.

Final Model

- Average Parameters:

  Vd (L/kg) = 2.54

  Ka (/hr)= 0.394

  $CL\ (L/hr/kg^{0.75}) = (CL_{birth}+CL_{maturation})*fCL_{2B6}*fCL_{induction}*fCL_{gest\ age}$

  Where:

  CL_{birth} is clearance at birth = 0.0439

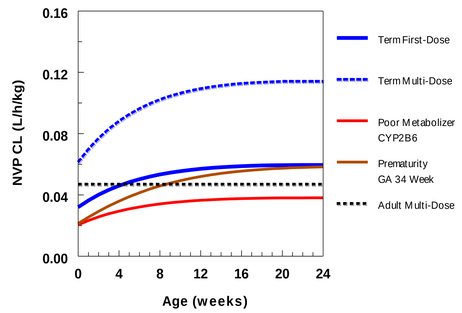
  $CL_{maturation}$ is clearance gain by age 12 months = 0.059
  ($t1/2$ of $CL_{maturation}$ is 5.6 weeks)

  fCL_{2B6} is reduction factor if CYP2B6 slow metabolizer (516TT) = 0.64
  (fCL_{2B6} estimated from literature[7])

  $fCL_{induction}$ is factor for NVP autoinduction = (NVP dose*0.0656)
  ($t1/2$ of $CL_{induction}$ = 70 hrs, estimated from literature[8])

  $fCL_{gest\ age}$ is reduction factor if premature = $0.935^{(40-\ gest\ age)}$
  ($fCL_{gest\ age}$ estimated from literature[9])

Impact of Factors Influencing NVP PK



- Interindividual Variability

  Vd: 79%

  CL: 79%

- Residual Error: 28%

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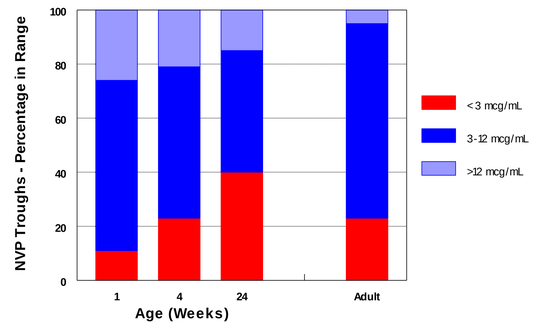
Results

NVP Trough Concentrations with Treatment Dose



Conclusions

- NVP CL is low immediately after birth and increases dramatically over the first 2 months of life.
- NVP CL undergoes autoinduction in proportion to dose size during the first year of life.
- NVP CL in infants may be impacted by CYP2B6 metabolizer status and prematurity.
- An understanding of the influences of these factors on infant NVP CL is necessary to develop an appropriate NVP dosing regimen in infants.
- Simulations with the dosing regimen of term infant doses of 6 mg/kg BID and late preterm infant doses of 4mg/kg BID for 1 week followed by 6 mg/kg BID achieved the NVP trough target of 3.0 ug/mL.

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