Background: Nevirapine (NVP) is eliminated primarily via hepatic metabolism by the cytochrome P450 enzymes 2B6 and 3A4. 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 autoregulation of the metabolic pathway, so that after 2 weeks of treatment NVP clearance increases 1.5 to 2 fold and mean elimination half life falls by 50%.

Methods: We developed a NVP population pk model using NONMEM that incorporated data for 192 infants (1112 plasma NVP conc) from US, Africa and Brazil. 1 yr in 5 PACTs 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 mcg/mL.

Results: A one compartment model with first order absorption was used. CL was scaled allosterically and volume of distribution (Vd) was scaled linearly with weight. CL was modeled to mature exponentially with age. Autoinduction of CL was modeled as a first order process. The effects of prematurity and maturation of CYP2B6 and CYP3A4 activity on NVP CL were imputed from published studies. Typical CL (10/7kg) in term infants increased by nearly 6 fold from birth to 6 months due to maturation and by an additional 75% due to induction. Final model used term infant dose of 6mg/kg BID and late preterm dose 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.

Abstract

Objective

To use population modeling of existing neonatal and infant NVP data 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 (thru age 3 months), studies in infants 1 month after birth, NVP pk studies under age 1 month have been limited to evaluations of dosing regimens for prophylaxis against HIV infection (thru age 0.1 mcg/mL). Lack of pk data and simulations can be used to evaluate proposed NVP dosing regimens to meet treatment target concentrations in term and late preterm infants (34-77 weeks gestation) from birth through 6 months of life.

Results

Subjects were infants under 1 year of age enrolled in one of 5 protocols: 1. PACT 250 – phase I study of NVP safety and pharmacokinetics after first single maternal intrapartum and infant postpartum doses in Ugandan pregnant women 2. HIVNET 006 - phase I study of NVP safety and pharmacokinetics after single maternal intrapartum and infant postpartum doses in Ugandan pregnant women 3. PACT 356 – phase II/I study of safety and pharmacokinetics of early intensive combination antiretroviral therapy in HIV infected infants 4. PACT 023 – phase II/I study of the safety and pharmacokinetics of NVP given as prophylaxis in breast feeding infants during the first 6 months of life. 5. PACT 020 - phase III randomized trial of the safety and efficacy of 3 neonatal antiretroviral regimens for prevention of mother to infant transmission.

• Subjects demographic and clinical characteristics, drug levels, and trough concentrations of NVP were analyzed.

• One compartment model with first order absorption, CL scaled allosterically and volume of distribution (Vd) scaled linearly with weight. NVP CL was scaled allometrically and volume of distribution (Vd) was scaled linearly with weight. CL was modeled to mature exponentially with age. Autoinduction of CL was modeled as a first order process.

• The effects of prematurity, CYP2B6 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
• CL (L/hr/kg) = 0.394
• CLreduction factor if premature = 0.935

Where:

• CLreduction factor if premature = 0.935

Impact of Factors Influencing NVP PK

NVP CL and Vd were imputed from published studies. Typical CL (L/hr/kg) in term infants was 0.394 L/hr/kg at birth and decreased in premature infants due to immaturity in CYP2B6 and CYP3A4 activity. 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 autoregulation of the metabolic pathway, so that after 2 weeks of treatment NVP clearance increases 1.5 to 2 fold and mean elimination half life falls by 50%.

Dosing and Sampling Regimens

1. PACT 250 – Intensive sampling - first week of life
   - 10 newborns – intrapartum maternal dosing only (100 or 200 mg)
   - 8 newborns – 200 mg maternal intrapartum dosing, single 2 mg/kg intrapartum dose at 48-72 hours
   - 10 newborns – prenatal maternal dosing for up to 14 days, 20 mg maternal intrapartum and infant postnatal 2 mg/kg dosing

2. HIVNET 006 – Intensive sampling – first week of life
   - 9 newborns – intrapartum maternal dosing only (200 mg)
   - 8 newborns – 200 mg maternal intrapartum dosing, single 2 mg/kg intrapartum dose at 48-72 hours

3. PACT 356 – Sparse sampling – 1 month – 1 year old
   - 45 infants, weekly pair of doses (1 or 2 doses) - for age range of 1 year of age received 120 mg/m2 p.o. for 14 days, then 200 mg/m2 q24h

4. HIVNET 023 – Sparse sampling at 2, 8, 16 and 24 weeks
   - 58 infants received daily, twice weekly or weekly dosing (2 or 4 mg/kgx4 doses, then 4 or 8 mg/kg by birth through 6 age months)

5. HPTN 020 – Intensive sampling (14 infants), Sparse sampling (30 infants) – first 2 weeks of life
   - 44 newborns – no maternal dosing, infant dosages within 48 hours of birth, 48 hours after the first dose and 96 hours after second dose

• Intratreatment Variability
   - CL: 79%

• Residual Error: 28%

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References


