Nevirapine Plasma Concentrations in Human Immunodeficiency Virus-Exposed Neonates Receiving High-Dose Nevirapine Prophylaxis as Part of 3-Drug Regimen

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We recently provided care for 3 human immunodeficiency virus (HIV)-exposed babies at high risk for perinatal acquisition of HIV. Since the first report of possible functional cure of 1 baby in Mississippi [1] with early triple-drug therapy of the newborn and the possible clearance of HIV from the peripheral blood of another infant [2], optimal management of high-risk, HIV-exposed infants is being reconsidered. Early initiation can suppress viremia and leads to a smaller number of infected cells as a reservoir for continued infection [3]. The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network is conducting a study to examine the potential utility of this approach for newborns exposed to HIV. Despite the recent information that the “Mississippi baby” has relapsed, there remains a need to evaluate the safety and effectiveness of high-dose nevirapine in neonates. Lack of such data for treatment doses of nevirapine in neonates complicates the potential enthusiasm for this approach. In this study, we present unique pharmacokinetic data on nevirapine plasma concentrations obtained in 3 newborns.

Case 1
A 34-year-old mother with unknown perinatal screening laboratory values, including HIV status, was transferred to our facility after she was found to have a reactive rapid HIV test. A repeat rapid HIV test was done at our hospital (OraQuick) and was positive. The mother received intravenous (IV) zidovudine for 4 hours before her C-section and delivered a healthy 38 0/7-week male infant, with a birth weight of 3.035 kg, who was considered to be at high risk for perinatal HIV acquisition because of possible recent maternal seroconversion. The infant received zidovudine 12 mg orally every 12 hours (4 mg/kg per dose) and lamivudine 6 mg orally every 12 hours (2 mg/kg per dose). In addition nevirapine 6 mg orally every 12 hours (2 mg/kg per dose) × 1 dose and subsequently changed to 18 mg orally every 12 hours (~6 mg/kg per dose). A trough plasma concentration of nevirapine was obtained because the length of therapy was uncertain. By day 5 of life, the maternal HIV enzyme-linked immunosorbent assay antibody, HIV viral load, and Western blot were reported as negative and all antiretroviral medications were discontinued. It was concluded that the initial rapid HIV test performed at delivery had been falsely reactive.

Case 2
A 33-year-old pregnant female with known HIV infection re-entered care 18 days before delivery at 34 weeks gestation. At this time, a urine drug screen was positive for amphetamines and marijuana. Given the late timing of initiation of antiretroviral therapy relative to the expected due date, the mother was started on zidovudine/lamivudine, lopinavir/ritonavir, and raltegravir to achieve rapid viral suppression. Her CD4 count was 339 (23%) and her HIV viral load was of 47 180 (copies/mL) at presentation.

When she was admitted for delivery, she reported having been in active labor for 72 hours already with good compliance with her antiretroviral therapy. Her urine remained positive for marijuana (but not for amphetamines) at the time of the delivery. She was started on IV zidovudine and received approximately 2 hours of therapy, before progression of labor necessitated a C-section given her presumed high viral load.

She delivered a 36 4/7 weeks gestation female infant, with a birth weight of 2.370 kg, who was started on zidovudine 7
mg IV (3 mg/kg per dose), given the short duration of maternal zidovudine. The baby was given oral lamivudine 5 mg (approximately 2 mg/kg per dose) every 12 hours and oral nevirapine 14 mg with a goal of approximately 6 mg/kg per dose every 12 hours started within the first 6 hours of life. All dosing was based on birth weight. The baby was given a second dose of IV zidovudine at 12 hours of life due to poor feeding and the high risk for perinatal transmission and was continued thereafter on zidovudine 9.5 mg (4 mg/kg per dose) orally every 12 hours. Because nevirapine dosing in premature infants is not known and duration of therapy was not known, we obtained a trough plasma concentration. Human immunodeficiency virus DNA polymerase chain reaction (PCR) at birth, 2 weeks of age, and 1, 2, and 6 months of age have been negative. Maternal viral load at the time of delivery subsequently was 228 copies/mL.

**Case 3**

A 30-year-old female gave birth to a 3.05 kg female infant with an estimated gestational age of 39 weeks at another hospital by normal spontaneous vaginal delivery. After delivery, the mother notified the obstetrics team that she was HIV positive, which was confirmed by a rapid test. Per initial report, the mother noted she was tested at her only prenatal visit at 4 months and found to be positive for HIV but did not seek further care for either her HIV or pregnancy. The mother also had a significant history for methamphetamine and marijuana abuse, as well as a history of syphilis treated in 2009, but a rise in titers in 2011 for which mother and public health report no further treatment of syphilis treatment history and a positive RPR, the baby was also treated for possible syphilis. Given the high risk of HIV transmission, we obtained a trough plasma concentration. Human immunodeficiency virus DNA PCR at birth and 2 weeks are negative. Maternal viral load 3 days after delivery was found to be 11 300 copies/mL.

**METHODS**

Plasma nevirapine concentrations were measured using a validated high-performance liquid chromatography-ultraviolet assay, based on the method of Pav et al [4] with an analytical range from 25 to 10 000 ng/mL. Samples below this range were reported as below the limit of quantitation, whereas samples with an initial concentration above 10 000 ng/mL were diluted with blank plasma and measured again. The performance of the assay was compliant with US Food and Drug Administration (FDA) guidelines with percent coefficient of variance and percent error limits less than 15% except at the lower limit of quantitation (25 ng/mL) where 20% was acceptable.

**RESULTS**

The nevirapine (NVP) trough plasma concentration (TPC) in the infant described in Case 1 preformed at 14 hours after the 4th dose of 18 mg (5.93 mg/kg per dose) was 5777 ng/mL. The NVP TPC in the infant presented in Case 2 at 12.25 hours after the 8th dose of 14 mg (5.9 mg/kg per dose) was 12 785 ng/mL. The NVP TPC in the infant presented in Case 3 at 11 hours after the 6th dose of 18.3 mg (6 mg/kg per dose) was 17 099 ng/mL. However, at 2 weeks of life after dose 30 of nevirapine 18.3 mg (6 mg/kg dose), the trough concentration had declined to 3002.5 ng/mL.

**DISCUSSION**

Nevirapine is presently approved for use in children ≥15 days of age. The recommended nevirapine dose for children <8 years of age is 200 mg/m² twice daily [5]. There are not sufficient pharmacokinetic data to provide a dose recommendation for infants ≤14 days of age and for premature infants. An ongoing study by the IMPAACT network for full-term, very high risk infants is examining treatment doses of nevirapine twice daily based upon pharmacokinetic modeling [5]. We believe our data will help inform this study.

A previous nevirapine pharmacokinetic study evaluated 639 children ranging in age from 0.3 to 8.3 years. Children received maintenance dosages of 120 to 200 mg/m² twice daily [6]. The objective of the study was to compare expected concentrations with a World Health Organization weight-based dosing approach to FDA dosing recommendations. Although exact summary statistics for trough concentrations were not given, the median measured trough (ie, 12 hours postdose) nevirapine concentration was approximately 5000 ng/mL, and concentrations seemed to range between 3000 ng/mL to slightly greater than 10 000 ng/mL. Based on adult dosing data, these investigators selected a target range for trough concentrations of 3000 ng/mL to 7630 ng/mL, using consensus recommendations that troughs above 3000 ng/mL are associated with a higher likelihood of therapeutic response [5], and that a value of 7630 ng/mL represents the 95th percentile of trough concentrations in adults [7]. However, there is no consensus on the maximum acceptable NVP.

With the NVP goals of 3000–7630 ng/mL, the infant in our first case fell within the range of goal NVP targets. This trough concentration might have been slightly low because it was drawn 14 hours after the 4th dose of nevirapine. The trough concentration in this infant may also have been lower because of the initial dose of nevirapine at 4 mg/kg before
switching to 6 mg/kg dosing. The infants in the second (12,785 ng/mL) and third case (17,099 ng/mL) had trough concentrations that were well above the goal range. However, the second infant’s level was still within the concentrations seen in the population pharmacokinetic study of infants [6]. Prematurity may have contributed to the elevated trough for Case 2, but it was not a factor for Case 3, a full-term infant. In Case 3, a second level was done because of the initially elevated trough concentration to determine whether the dose should be adjusted after enzyme induction and was significantly lower at 3002.5 ng/mL.

CONCLUSIONS

Determination of appropriate dosing for infants, and especially premature infants, based on prospectively collected pharmacokinetic testing, would be a valuable contribution to the literature and would improve patient care. Clinicians using the 3-drug regimen for neonates should be aware of the lack of systematic data on the pharmacokinetics and safety of high-dose nevirapine in newborns. We recommend, if feasible, checking NVP trough plasma concentrations to ensure efficacy but more importantly to avoid unwanted toxicity in these at-risk infants. Furthermore, there is a lack of understanding of the ontogeny of the drug-metabolizing pathways involved in nevirapine clearance in infants, complicated because nevirapine is an inducer of its own metabolism. Therefore, there is a need for pharmacokinetic data in these infants at later time points. Induction of metabolism in infants may or may not mirror that seen in older children and adults. Given the limited observational data, we are unable to define a specific treatment dose of nevirapine for at-risk newborns. We encourage further study of this promising regimen.

Note
Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References