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Nevirapine

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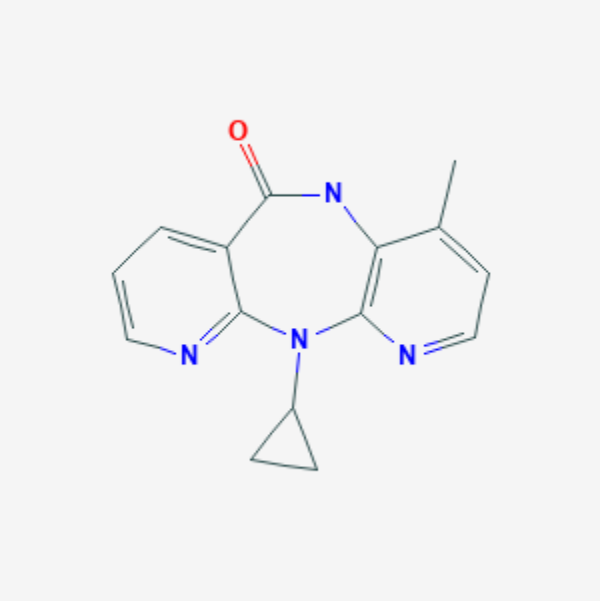

Drug Levels and Effects

Summary of Use during Lactation

In the United States and other developed countries, HIV-infected mothers should generally not breastfeed their infants. Nevirapine has been well studied in nursing mothers. In countries in which no acceptable, feasible, sustainable and safe replacement feeding is available, World Health Organization guidelines recommend that all women with an HIV infection who are pregnant or breastfeeding should be maintained on antiretroviral therapy for at least the duration of risk for mother-to-child transmission. Mothers should exclusively breastfeed their infants for the first 6 months of life; breastfeeding with complementary feeding should continue through 12 months of life. The first choice regimen for nursing mothers is tenofovir, efavirenz and either lamivudine or emtricitabine. If these drugs are unavailable, alternative regimens include: 1) zidovudine, lamivudine and efavirenz; 2) zidovudine, lamivudine and nevirapine; or 3) tenofovir, nevirapine and either lamivudine or emtricitabine. Exclusively breastfed infants should also receive 6 weeks of prophylaxis with nevirapine.[1,2]

Because of the long half-life of nevirapine, subtherapeutic nevirapine concentrations can persist in breastmilk and infant serum for relatively long periods, potentially increasing the risk of development of nevirapine-resistant HIV infections when it is used alone for prophylaxis in the mother.[3-8]

Drug Levels

Maternal Levels. Four breastmilk samples were obtained from 3 mothers who were taking nevirapine either 100 mg or 200 mg daily. Milk concentrations averaged 76% (range 54 to 104%) of maternal serum concentrations.[9]

Twenty-one women received a single 200 mg oral dose of nevirapine during labor. Milk samples were collected 48, 72 and 168 hours after the dose. Breastmilk concentration of nevirapine were 454 mcg/L (range 219 to 972 mcg/L) at 48 hours postpartum and declined to 103 mcg/L (range 25 to 309 mcg/L) at 7 days postpartum. Milk levels declined in parallel with the maternal serum concentration with a half-life averaging 61 hours.[10]

Three women were receiving nevirapine 200 mg twice daily as part of a highly active antiretroviral combination regimen. During the first 5 days postpartum milk was collected just before and 2 hours after the dose of nevirapine. Breastmilk nevirapine concentrations from milk samples ranged between 68 and 90% of the maternal serum concentration. Further details on the timing, or actual breastmilk concentrations were not provided.[11]

Twenty women who were receiving oral nevirapine 200 mg twice daily as part of a combination antiretroviral regimen had their milk analyzed at either 2 or 5 months postpartum. Milk samples were provided at a median of 4 hours (range 1 to 8.5 hours) after the last dose. The median nevirapine concentration in breastmilk was 6.8 mg/L.[12]

Forty women were given postpartum prophylaxis with unstated dosages of lamivudine, nevirapine and zidovudine (or stavudine if the hemoglobin <8 g/dL). Blood and milk samples were collected once during the first 3 days postpartum and once at 7 days postpartum. The median times after a dose that samples were collected were 5.3 hours (range 0 to 99 hours) for the first sample and 6 hours (range 4.3 to 20 hours) for the 7-day sample. Average breastmilk nevirapine concentrations were calculated only for samples that had detectable (>50 mcg/L) concentrations of nevirapine. The mean breastmilk concentrations were 2.3 (n = 34) and 2.2 mg/L (n = 36), respectively, at the two sampling times, which was 60 to 80% of the simultaneous maternal serum concentrations.[13]

Free and total breastmilk nevirapine concentrations were measured in one woman for 22 days after her last dose of nevirapine 200 mg which was given as part of a combination antiretroviral regimen to prevent mother-to-child transmission of HIV. The peak whole milk concentration was 2.7 mg/L. Nevirapine was detectable in whole breastmilk for up to 17 days after the dose with an average (of left and right breasts) concentration of 13 mcg/L at that time. The average half-life was 70.6 hours. The peak unbound milk concentration was 1.5 mg/L. Nevirapine was detectable in whole breastmilk for up to 13 days after the dose with an average (of left and right breasts) concentration of 15.5 mcg/L at that time. The average half-life was 58 hours.[14]

Twenty-one samples of breastmilk and maternal serum were obtained at 6, 12 and 24 weeks postpartum from mothers taking nevirapine as part of a combination of antiretrovirals. The nevirapine dosage the mothers were taking was not stated in the abstract. The median breastmilk concentrations of nevirapine were 1.3 mg/L at a median of 15 hours after the last dose at 6 weeks postpartum (8 samples), 3.4 mg/L at a median of 13 hours after the last dose at 12 weeks postpartum (7 samples), and 1.2 mg/L at a median of 12 hours after the last dose at 24 weeks postpartum (6 samples). Median milk concentrations were 12% (interquartile range 0 to 30%) of maternal plasma concentrations.[15] In a related study by the same authors, the nevirapine milk to plasma ratio was found to be 0.82 in 39 patients.[16]

Fifty-eight mothers who were taking a combination regimen of lamivudine, nevirapine and zidovudine had their serum and breastmilk analyzed for the presence of these drugs. Mothers took nevirapine 200 mg daily for 14 days, then 200 mg twice daily starting at 34 to 36 weeks postpartum and continuing until 6 months postpartum. Breastmilk was collected within 24 hours after delivery and at 2, 6, 14 and 24 weeks postpartum at variable times after the previous dose. The median breastmilk lamivudine concentration across all visits was 4546 mcg/L. The authors estimated that a fully breastfed infant would receive a daily dosage of 682 mcg/kg of nevirapine.[17]

Sixty-two women received a single 200 mg dose of nevirapine at a median time of 5.2 hours before delivery. Breastmilk was obtained from each breast at delivery and 1, 2, and 6 weeks after the dose. A total of 116 breastmilk samples were obtained and analyzed. At delivery, the median breastmilk nevirapine concentration was 1012 mcg/L (interquartile range [IQR] 657 to 1364 mcg/L). At 1 week postpartum, breastmilk nevirapine had a median concentration of 164 mcg/L (IQR 75 to 213 mcg/L); breastmilk obtained 13 to 16 days postpartum had a median nevirapine concentration of 17 mcg/L (IQR 15 to 35 mcg/L). Nevirapine was undetectable (<15 mcg/L) in breastmilk at 6 weeks postpartum. Maternal plasma and breastmilk nevirapine concentrations fell with a half-life of 50.3 hours. A pharmacokinetic simulation indicated that breastmilk nevirapine concentrations fell below the IC50 for HIV at a median of 17 days (range 11.25 to 25.8 days) postpartum.[4]

Milk samples were analyzed for nevirapine after mothers took a single 200 mg dose of nevirapine at the onset of labor. Of 51 mothers' milk samples, 47 had detectable nevirapine one week after taking the dose, with a median concentration of 112 mcg/L. At 2 weeks after the dose, the median concentration was 15 mcg/L in 40 milk samples assayed. At 4 weeks, nevirapine was undetectable (<10 mcg/L) in all 43 samples assayed.[18]

Fifty-seven mothers who were receiving nevirapine 200 mg twice daily as part of a combination antiretroviral regimen provided a total of 181 milk samples at birth, 1 month, 3 months and/or 6 months postpartum. Milk samples were collected at a median of 4.5 hours (range 3.5 to 6 hours) after the previous dose. The median breastmilk nevirapine concentration was 2901 mcg/L (range 2097 to 4684 mcg/L).[19]

Fifteen women had been taking nevirapine 200 mg twice daily as part of one of three drug combinations. Breastmilk samples were collected at just before a dose at a median of 1 month postpartum. Whole breastmilk levels contained a median of 1.83 mg/L of nevirapine, which was a median of 27% of maternal blood levels.[20]

From a study of 224 women who received a single dose of nevirapine 200 mg at delivery, 1212 breastmilk samples were obtained at either 1 week and/or 4 weeks postpartum. At 1 week postpartum, nevirapine was detectable in 98% of women with median concentration of 0.22 mg/L. At 4 weeks, nevirapine was not detectable in breastmilk.[21]

Five HIV-positive nursing mothers taking nevirapine 200 mg every 12 hours provided breastmilk samples 0.5, 1, 2, 4, 8 and 12 hours after a dose. Mean peak and trough nevirapine concentrations in breastmilk were 5.2 mg/L and 4.3 mg/L, respectively. The trough values occurred at 0.5 hours after the dose and peak values occurred at 4 hours after the dose.[22]

Twenty-eight women who were receiving nevirapine 200 mg twice daily and had genetic variations in CYP2B6 had various pharmacokinetic parameters calculated related to drug excretion into breastmilk. Three polymorphisms in this enzyme resulted in differing amounts of nevirapine excreted into breastmilk, apparently related to differences in maternal plasma concentrations. These differences were reflected varying infant plasma nevirapine concentrations.[23]

Infant Levels. Twenty nursing mothers were receiving oral nevirapine 200 mg twice daily as part of a combination antiretroviral regimen. Their infants had serum concentrations determined at either 2 or 5 months postpartum. Serum samples were provided at a median of 4 hours (range 1 to 8.5 hours) after the last dose. The median infant serum nevirapine concentration was 971 mcg/L (range <16 to 2191 mcg/L). The average value was 40 times the IC50 for HIV.[12]

The infants of postpartum mothers taking nevirapine as part of a combination of antiretrovirals had undetectable serum nevirapine concentrations by HPLC/MS analysis. The nevirapine dosage the mothers were taking and times of infant plasma sampling were not stated in the abstract. Infant serum concentrations were measured at 6 (8 samples), 12 (7 samples), and 24 (6 samples) weeks of age at averages of 15, 13 and 12 hours after the last maternal dose. Median infant serum nevirapine concentrations were 584, 607 and 233 mcg/L, respectively, which was 12% of the maternal serum concentration.[15]

Fifty-eight infants whose mothers were taking a combination regimen of lamivudine, nevirapine and zidovudine had their serum analyzed for the presence of these drugs. Mothers took nevirapine 150 mg twice daily starting at 34 to 36 weeks postpartum and continuing until 6 months postpartum and were instructed to exclusively breastfeed for 5.5 months. Serum samples were collected within 24 hours after delivery and at 2, 6, 14 and 24 weeks postpartum. The median infant dried blood spot nevirapine concentrations were 2963 mcg/L at delivery, 987 mcg/L at week 2, 1032 mcg/L at week 6, 734 mcg/L at week 14 and 303 mcg/L at week 24 postpartum.[17]

Breastfed infants of 58 mothers who were receiving nevirapine 200 mg twice daily as part of a combination antiretroviral regimen had a total of 58 blood samples analyzed at 1 month, 3 months and/or 6 months postpartum. Samples were collected at a median of 4.5 hours (range 3.5 to 6 hours) after the previous maternal dose and a median of 30 minutes (range 20 to 60 minutes) after the previous nursing. The infants' median nevirapine plasma concentration was 809 mcg/L (range 535 to 1061 mcg/L, which was a median of 18% (range 14 to 24%) of the maternal serum concentration.[19]

Nine infants were breastfed either partially or exclusively by their mothers who had been taking nevirapine 200 mg twice daily as part of a drug combination that included zidovudine and lamivudine. Infant blood was collected at a median of 1 month postpartum at 12 to 17 hours after the last dose and a median of 1 hour (range 6 minutes to 35 hours) after the last breastfeeding. All nine infants had detectable nevirapine levels in their serum, with a median concentration of 0.37 mg/L (range 0.24 to 1.2 mg/L).[20]

Four HIV-positive nursing mothers were taking nevirapine 200 mg every 12 hours. Their breastfed infants had serum nevirapine concentrations of 529 mcg/L and 556 mcg/L, at 2 and 8 h after the maternal dose, respectively.[22]

Effects in Breastfed Infants

A study assigned pregnant women to zidovudine alone or highly-active antiretroviral therapy (HAART: zidovudine, lamivudine and nevirapine) to prevent maternal-to-child transmission of HIV infection. After delivery, All infants received one month of zidovudine prophylaxis; some infants were breastfed and others were formula fed. A higher percentage of infants in the HAART-exposed group had neutropenia than those in the unexposed group at 1 month of age (15.9 and 3.7%, respectively). Hematologic toxicity was transient and asymptomatic. From 2 to 6 months postpartum, no differences in hematologic toxicity were seen between breastfed and formula-fed infants. No statistical difference in hepatic toxicity was seen between the breastfed and formula-fed infants.[24]

A study compared the breastfed infants of women who received a HAART regimen with nevirapine (n = 270) to one that contained nelfinavir (n = 206) as an alternative. Both regimens also contained zidovudine and lamivudine. Moderate rash was slightly more prevalent in infants who received nevirapine than nelfinavir via breastmilk. No differences were found in the rates of severe rash, liver toxicity or hyperbilirubinemia.[25]

A study compared the frequency of rash, hepatotoxicity, and hyperbilirubinemia among 464 breastfed infants whose mothers were taking either nevirapine (n = 258) or nelfinavir (n = 206) along with zidovudine and lamivudine for HIV infection during pregnancy and postpartum. Infants were examined during the first, second and sixth weeks postpartum. Moderate rash occurred in 7 (2.7%) of the infant exposed to nevirapine and one (0.5%) infant exposed to nelfinavir. Rash occurred at a median of 2 weeks postpartum. Four infants (1.9%)

exposed to nelfinavir developed hepatotoxicity (3 moderate and 1 severe) and none exposed to nevirapine. Twenty-one infants (4.5%) developed high-risk hyperbilirubinemia, all prior to 48 hours of age, but there was no difference in exposure between the two drugs.[26]

Effects on Lactation and Breastmilk

Hyperprolactinemia and galactorrhea occurred in a woman on a combination antiretroviral regimen after nevirapine was substituted for nelfinavir. Galactorrhea ceased rapidly after nevirapine was discontinued.[27] The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

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Substance Identification

Substance Name

Nevirapine

CAS Registry Number

129618-40-2

Drug Class

Breast Feeding

Lactation

Anti-Infective Agents

Anti-HIV Agents

Antiviral Agents

Anti-Retroviral Agents

Reverse Transcriptase Inhibitors