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Efavirenz

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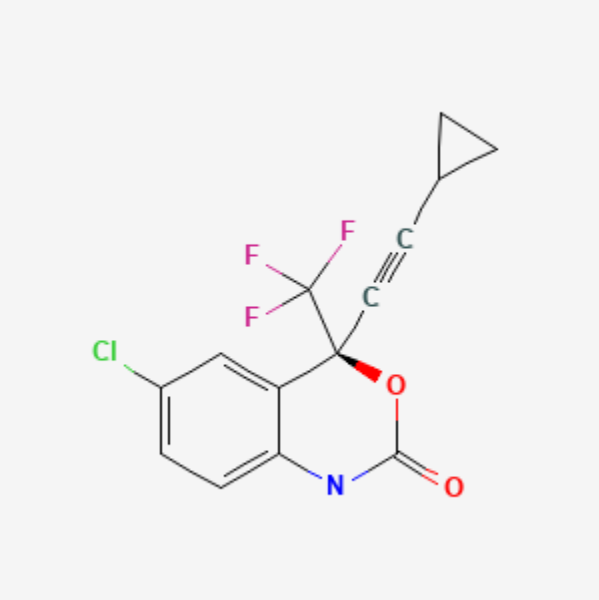

Drug Levels and Effects

Summary of Use during Lactation

Efavirenz is excreted into breastmilk and small amounts are found in the serum of some infants. Treatment of mothers of HIV-positive mothers with efavirenz does not appear to affect growth and development of their HIV-negative breastfed infants. Achieving and maintaining viral suppression with antiretroviral therapy decreases breastfeeding transmission risk to less than 1%, but not zero. Individuals with HIV who are on antiretroviral therapy with a sustained undetectable viral load and who choose to breastfeed should be supported in this decision. If a viral load is not suppressed, banked pasteurized donor milk or formula is recommended.[1,2]

Drug Levels

Maternal Levels. Thirteen mothers who averaged 15.8 weeks (range 6 to 25 weeks) postpartum were treated with efavirenz 600 mg daily plus zidovudine and lamivudine. Milk and plasma samples were taken 3 to 4 hours after the last dose. Skimmed breastmilk efavirenz concentrations averaged 3.5 mg/L (range 1.3 to 7.4 mg/L).[3]

Five mothers who were taking oral efavirenz 600 mg daily as part of an antiretroviral regimen collected mid-feed milk samples at 0.5, 1, 2, 4, 8, 12 and 24 hours after an evening dose at an average of 146 days after delivery. The average peak level of 4.5 mg/L occurred at about 4 hours after the dose and the average trough milk value was 2.5 mg/L.[4]

One hundred thirty-four mothers who were taking efavirenz 600 mg at bedtime as part of their antiretroviral regimen and their infants were studied. In the first part of the study, women were separated into noncarriers, homozygotes and homozygotes for the CYP2B6 516TT gene. Random breastmilk concentrations had median values of 1610, 2370 and 4070 mcg/L in the three groups, respectively. A pooled subset of 29 mothers underwent extensive sampling of plasma and breastmilk sampling, encompassing 203 paired maternal plasma and breastmilk levels. In these mothers the median peak breastmilk levels were 4020 4540 and 8920 mcg/L, respectively. Corresponding trough milk levels were 1120, 1500, and 2480 mcg/L. The authors estimated that the average dosages that infants would receive would be 344 mcg/kg, 379 mcg/kg and 1340 mcg/kg daily in the maternal noncarrier, heterozygous and homozygous groups, respectively.[5] A physiologically based pharmacokinetic model was created by the authors and compared to the 29 pooled patients' data. Over 80% of observed data points were within the model's predictive interval.[6] Another model based on data from this study found that the simulated average milk concentrations were 2.31 mg/L, 2.89 mg/L and 4.63 mg/L from CYP2B6 516GG, GT, and TT mothers, respectively. These translated to average daily infant dosages of 0.35, 0.43, and 0.69 mg/kg, respectively.[7]

Women in Malawi received the option B+ regimen for prevention of mother-to-child transmission of HIV consisting of tenofovir, lamivudine and efavirenz between 6 and 8 pm daily. The efavirenz dose was not stated, but was presumably 600 mg daily. Milk samples collected in the morning from 33 women at month 1 postpartum had a median efavirenz concentration of 1.6 mg/L (IQR 0.86 to 2.3 mg/L). Milk samples collected in the morning from 47 women at month 12 postpartum had a median efavirenz concentration of 1.8 mg/L (IQR 1.0 to 4.3 mg/L).[8]

Mother-infant pairs were studied among mothers taking efavirenz 600 mg daily as part of a multi-drug HIV regimen. Mothers hand-express milk samples 12 to 14 hours after a morning dose at 1, 3 and 6 months postpartum. Median breastmilk efavirenz concentrations at 1, 3, and 6 months were 4.66 mg/L (n = 22) , 4.16 mg/L (n = 31) and 3.92 mg/L (n = 30), respectively. The weight-adjusted infant dosage was calculated to be 2.46% at 6 months.[9]

Three mothers taking efavirenz 600 mg once daily provided milk samples at a median of 18 hours after a dose. The median drug concentration in milk was 2701 mcg/L, which resulted in an estimated infant dosage of 0.41 mg/kg daily and a relative infant dose of 1.35% of the maternal weight-adjusted dosage.[10]

Infant Levels. Thirteen mothers who averaged 15.8 weeks (range 6 to 25 weeks) postpartum were treated with efavirenz 600 mg daily plus lamivudine and zidovudine (n = 12) or stavudine (n = 1). Plasma samples were taken from their breastfed infants 3 to 4 hours after the last dose. Infant plasma concentrations averaged 0.86 mg/L (range 0.4 to 1.5 mg/L). Infant plasma concentrations averaged 13% of maternal plasma concentrations, but there was no statistically significant correlation between them. Average plasma levels were slightly below the plasma level considered effective for suppression of HIV in adults.[3]

Efavirenz was measured in 117 breastfed (90% exclusive) infants whose mothers were taking efavirenz for HIV infection during pregnancy and postpartum. All infants had detectable efavirenz in their plasma samples at 0

(mean 1.7 mg/L), 8 (mean 0.3 mg/L) and 12 (mean 0.3 mg/L) weeks postpartum. All infants had detectable efavirenz in their hair samples at 12 weeks postpartum at a mean concentration of 1.9 mcg/gram of hair (range 0.34 to 11 mcg/gram). The authors interpreted the results to mean that infants receive substantial exposure to efavirenz during breastfeeding.[11]

One hundred thirty-four mothers who were taking efavirenz 600 mg at bedtime as part of their antiretroviral regimen and their infants were studied. In the first part of the study, women were separated into noncarriers, homozygotes and homozygotes for the CYP2B6 516TT gene. Random infant serum concentrations had median values of 124, 164, and 333 mcg/L in the three groups, respectively. A subset of mothers and infants underwent extensive sampling of plasma and breastmilk sampling. In these infants, median plasma levels were 166, 89 and 293 mcg/L at 2 hours after the maternal dose and 134, 86 and 342 mcg/L at 8 hours after the maternal dose, respectively.[5]

Blood samples were taken from 25 breastfed infants of mothers who were receiving option B+ regimen for prevention of mother-to-child transmission of HIV consisting of tenofovir, lamivudine and efavirenz between 6 and 8 pm daily. The efavirenz dose was not stated, but was presumably 600 mg daily. The median morning infant plasma concentration of efavirenz at 6 months of age was 86.4 mcg/L (IQR 0 to 329 mcg/L). The median morning infant plasma concentration of efavirenz at 12 months of age was 0 mcg/L.[8]

Mother-infant pairs were studied among mothers taking efavirenz 600 mg daily as part of a multi-drug HIV regimen. Infants were breastfed (extent not stated) and plasma concentrations were measured postpartum. Median plasma efavirenz concentrations at 1, 3, and 6 months were 347 mcg/L (n = 22), 268 mcg/L (n = 30), and 175 mcg/L (n = 17), respectively. These plasma concentrations ranged from 4.8% to 7.2% of simultaneous maternal plasma levels.[9]

An infant was breastfed by a mother taking efavirenz 600 mg once daily, although the extent of breastfeeding was not sated. The infant's serum concentrations taken 17 hours after maternal drug intake at 1 month of age was 267 mcg/L.[10]

Effects in Breastfed Infants

Thirteen mothers nursed their infants while they were taking efavirenz 600 mg daily, lamivudine 150 mg and zidovudine 300 mg daily (n = 12) or stavudine 60 mg daily (n = 1) . No adverse reactions were reported in the infants after 6 months of breastfeeding, none had developed HIV infection and all were developing normally.[3]

An unblinded study in Uganda compared the outcomes of breastfed infants and their HIV-positive mothers who were randomized to receive antiretroviral therapy that was based either on efavirenz 600 mg once daily or lopinavir 400 mg plus ritonavir 100 mg twice daily during breastfeeding. All mothers received lamivudine 150 mg, zidovudine 300 mg twice daily and trimethoprim-sulfamethoxazole once daily. All infants received prophylaxis with either zidovudine for 1 week or nevirapine for 6 weeks, plus trimethoprim-sulfamethoxazole from 6 weeks of age to 6 weeks after weaning. Almost all of the infants were exclusively breastfed until 6 months of age and about 73% were partially breastfed until 12 months of age. There was no statistical difference in hospitalizations or adverse events including anemia, neutropenia or deaths among infants in the two groups.[12]

Among 32 breastfed (extent not stated) infants whose mothers were taking efavirenz 600 mg daily as part of a multi-drug treatment for HIV infection, no adverse effects were noted by investigators or reported by mothers at 1, 3 and 6 months of age.[9]

A prospective cohort study in Malawi compared the infants of HIV+ mothers taking efavirenz and tenofovir disoproxil fumarate (n = 260) to infants of mothers who were HIV negative (n = 125). Infants were followed for growth and development for up to 18 months at which time there were 169 mother-infant pairs in the treatment

group and 54 in the HIV-negative group. No difference was found in the growth and development of the breastfed infants of treated women compared to the infants of untreated mothers.[13]

An open-label, controlled, multicenter phase 3 trial women who were confirmed HIV-positive were randomized to receive one of 3 regimens: dolutegravir, emtricitabine, and tenofovir alafenamide (n = 208); dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (n = 202); or efavirenz, emtricitabine, and tenofovir disoproxil fumarate (n = 207). The regimens were started at 14 to 28 weeks of pregnancy and continued postpartum. Of the 617 liveborn infants, 99% were breastfeeding at time of last infant HIV test, which was as late as 50 weeks of age. The mean infant duration on the study was 47.6 weeks of age. Infants who had any clinical or laboratory adverse event of grade 3 or higher ranged from 25 to 31%, but was not statistically significant between groups. Dolutegravir-containing regimens resulted in lower rates of virological failure, HIV drug resistance, and infant mortality up to 50 weeks postpartum compared with efavirenz, emtricitabine, and tenofovir disoproxil fumarate. [14]

Effects on Lactation and Breastmilk

Gynecomastia has been reported among men and at least one woman receiving efavirenz therapy.[15,16] Efavirenz appears to be much more likely to cause gynecomastia than other antiretroviral agents. Gynecomastia is unilateral initially, but can progress to bilateral. Spontaneous resolution usually occurred within one year, even with continuation of the regimen. The relevance of these findings to nursing mothers is not known. The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

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Substance Identification

Substance Name

Efavirenz

CAS Registry Number

154635-17-3

Drug Class

Breast Feeding

Lactation

Milk, Human

Anti-Infective Agents

Antiviral Agents

Anti-HIV Agents

Anti-Retroviral Agents

Reverse Transcriptase Inhibitors