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Lamivudine

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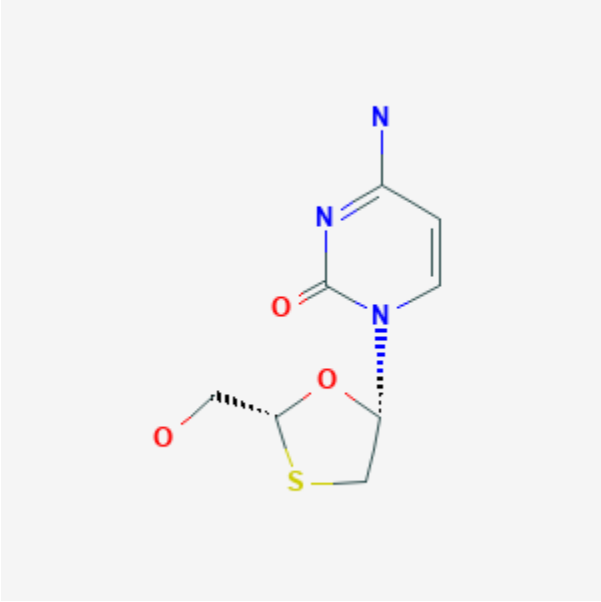

Drug Levels and Effects

Summary of Use during Lactation

Lamivudine has not been studied in HIV-negative nursing mothers being treated for hepatitis B infection, but the low doses used would not be expected to cause any serious adverse effects in breastfed infants. The manufacturer estimates that a breastfed infant's dose would be about 6% of the infant dose for children over 2 years of age. An expert review of available data concluded that there is currently no justification for contraindicating the use of lamivudine for hepatitis B therapy during breastfeeding.[1] Some professional organization guidelines allow breastfeeding during lamivudine therapy, although one guideline cautions against it because of a lack of long-term safety data.[2][3][4] The lack of long-term safety data with long-term, low-level infant exposure should be discussed with the mother.[2] No differences exist in infection rates between breast-fed and formula-fed infants born to hepatitis B-infected women, as long as the infant receives hepatitis B

immune globulin and hepatitis B vaccine at birth. Mothers with hepatitis B are encouraged to breastfeed their infants after their infants receive these preventative measures.[5][6]

In the United States and other developed countries, HIV-infected mothers should generally not breastfeed their infants. 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 at least 12 months of life up to 24 months of life.[7] 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.[8][9]

Drug Levels

Maternal Levels. Milk samples were taken daily before breastfeeding from 2 groups of women receiving lamivudine, one on monotherapy and the other on combination therapy. In the group receiving lamivudine 300 mg twice daily (n = 10), the average milk concentration was 1.2 mg/L (range <0.5 to 6.1 mg/L). In the group receiving 150 mg twice daily plus zidovudine (n = 10), the average milk lamivudine concentration was 0.9 mg/L (range <0.5 to 8.2 mg/L).[10]

Twenty women who were receiving oral lamivudine 150 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 lamivudine concentration in breastmilk was 1.8 mg/L.[11]

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 lamivudine concentrations were calculated only for samples that had detectable (>20 mcg/L) concentrations of lamivudine. The mean breastmilk concentrations were 0.4 (n = 9) and 0.4 mg/L (n = 30), respectively, at the two sampling times, which was 2.9 to 3.3 times the simultaneous maternal serum concentrations.[12]

Forty-seven samples of breastmilk and maternal serum were obtained at 6, 12 and 24 weeks postpartum from mothers taking lamivudine as part of a combination of antiretrovirals. The lamivudine dosage the mothers were taking was not stated in the abstract. The median breastmilk concentrations of lamivudine at a median of 14 hours after the last maternal dose were 510 (17 samples), 387 (17 samples) and 310 mcg/L (13 samples). Median milk concentrations were 2.6 times (interquartile range 1.1 to 3.5 times) the maternal plasma concentrations.[13] In a related study by the same authors, the lamivudine milk to plasma ratio was found to be 2.96 in 49 patients.[14]

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 lamivudine 150 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 for 153 samples across all visits was 1214 mcg/L. The authors estimated that a fully breastfed infant would receive a daily dosage of 182 mcg/kg of lamivudine.[15]

Sixty-six mothers who were receiving lamivudine 150 mg twice daily as part of a combination antiretroviral regimen provided a total of 206 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 lamivudine concentration was 446 mcg/L (range 269 to 683 mcg/L).[16] In a continuation of the same study, 65 breastmilk samples obtained at 1, 3 and 6 months postpartum were analyzed for lamivudine after the same dose. The median concentration was 684 mcg/L (IRQ range 405 to 868 mcg/L). It is not clear if the latter study included some of the same patients as the first study.[17]

Fifteen women had been taking lamivudine 150 mg twice daily for 53 to 182 days as part of a drug combination that included either abacavir and zidovudine or lopinavir, ritonavir, and zidovudine. Breastmilk samples were collected at just before a dose at a median of 1 month postpartum. Whole breastmilk levels contained a median of 0.14 mg/L of lamivudine, which was a median of 74% of maternal blood levels.[18]

Thirty women were studied at 6, 12 or 24 weeks postpartum (10 at each time). Each mother was taking zidovudine 300 mg, lamivudine 150 mg, lopinavir 400 mg, and ritonavir 100 mg twice daily by mouth starting at delivery. On the study day, at a median of 14.9 hours after the previous evening's dose, maternal plasma and breastmilk samples were obtained prior to the morning dose and 2, 4 and 6 hours after the dose. One hundred seven of the 121 breastmilk samples contained detectable quantities (10 mcg/L or greater) of lamivudine, with an median breastmilk concentration of 0.94 mg/L over the 6 hours.[19]

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 lamivudine dose was not stated, but was presumably 300 mg daily. Milk samples collected in the morning from 33 women at month 1 postpartum had a median lamivudine concentration of 537 mcg/L (IQR 369 to 768 mcg/L). Milk samples collected in the morning from 47 women at month 12 postpartum had a median lamivudine concentration of 430 mcg/L (IQR 266 to 531 mcg/L).[20]

Lamivudine was measured in 6 HIV-positive nursing mothers during ongoing therapy with a dosage of 150 mg every 12 hours. A peak breastmilk level of 994 mcg/L (range 958-1274 mcg/L) was reached at 2 to 4 hours after the dose.[21]

Thirty-nine Nigerian and Ugandan women took lamivudine 150 mg twice daily (n = 11) or 300 mg once daily in the morning (n = 10) or previous evening (n = 18) as part of a combination therapy for HIV. Expressed milk samples were taken before the dose and at 0.5, 1, 2, 4, and 8 hours after the morning dose of 150 or 300 mg or samples between 12 to 20 hours after the 300 mg evening dose. The median peak breastmilk concentration from dried breastmilk spots in mothers taking 150 mg twice daily was 908 mcg/L (IQR 772 to1015 mcg/L) at a median of 6 hours after the dose (IQR 4 to 6 hours). The median peak breastmilk concentration from dried breastmilk spots in mothers taking 300 mg once daily was 663 mcg/L (IQR 445 to 890 mcg/L) at a median of 6 hours after the dose (IQR 4 to 8 hours).[22]

Nine HIV-positive women about to undergo cesarean section received 3 doses of lopinavir 200 mg, ritonavir 150 mg, zidovudine 300 mg, lamivudine 50 mg at 3 hour intervals before the procedure. Breastmilk samples were collected at a mean of 25 hours postpartum. In the 8 women where it was quantified, the average milk concentration of lamivudine was 449 mcg/L (range 143 to 1148 mcg/L).[23]

Infant Levels. Twenty nursing mothers were receiving oral lamivudine 150 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 lamivudine concentration was 28 mcg/L (range <14 to 53 mcg/L). The average value was 5% of the IC50 for HIV.[11]

The infants of postpartum mothers taking nevirapine as part of a combination of antiretrovirals had undetectable serum nevirapine concentrations by HPLC/MS analysis. The lamivudine dosage the mothers were taking and times of infant plasma sampling were not stated in the abstract. Infant serum concentrations were measured at 6 (17 samples), 12 (17 samples), and 24 (13 samples) weeks of age at an average of 14 hours after the last maternal dose. Median infant serum lamivudine concentrations were 13, 10, and 5 mcg/L, respectively, which was 6% of the maternal serum concentration.[13]

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 lamivudine 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 lamivudine concentrations were 67 mcg/L at delivery, 32 mcg/L at week 2, 24 mcg/L at week 6, 20 mcg/L at week 14 and not measurable (<16 mcg/L) at week 24 postpartum.[15]

Breastfed infants of 66 mothers who were receiving lamivudine 150 mg twice daily as part of a combination antiretroviral regimen had a total of 64 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 median infants' lamivudine plasma concentration was 18 mcg/L (range 7 to 35 mcg/L), which was a median of 2% (range 0 to 4%) of the maternal serum concentration.[16] In a continuation of the same study, 17 breastfed infants (extent not stated) donated 22 blood samples between 1 and 6 months for lamivudine analysis. Their mothers were taking lamivudine 150 mg twice daily as part of combination antiretroviral regimens. The median concentration was 29.2 mcg/L (IRQ range 12.2 to 58.7 mcg/L). It is not clear if the latter study included some of the same patients as the first study.[17]

Twenty-four infants were breastfed either partially or exclusively by their mothers who had been taking lamivudine 150 mg twice daily for 53 to 182 days as part of a drug combination that included either abacavir and zidovudine or lopinavir, ritonavir, and zidovudine. Infant blood was collected at a median of 1 month postpartum at 11 to 18 hours after the last dose and a median of 1 hour (range 6 minutes to 35 hours) after the last breastfeeding. All of the infant plasma samples had undetectable (<7 mcg/L) plasma levels of lamivudine.[18]

Thirty nursing mothers were studied at 6, 12 or 24 weeks postpartum (10 at each time). Each mother was taking lamivudine 150 mg twice daily by mouth starting at delivery. Infant plasma samples were obtained before their mother's first dose and at 2, 4 and 6 hours after the mother's dose. Infants were allowed to breastfeed *ad libitum* during the study period. Lamivudine was detectable (10 mcg/L or greater) in 107 of the 115 infant plasma samples, at a median concentration of 180 mcg/L.[19]

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 lamivudine dose was not stated, but was presumably 300 mg daily. The median morning infant plasma concentration of lamivudine at 6 months of age was 2.5 mcg/L (IQR 2.5 to 7.6 mcg/L). The median morning infant plasma concentration of lamivudine at 12 months of age was 0 mcg/L.[20]

Lamivudine 150 mg twice daily was given to 6 HIV-positive nursing mothers. Two of their breastfed infants had detectable lamivudine serum levels of 13.2 and 15.6 mcg/L.[21]

Thirty-nine Nigerian and Ugandan women took lamivudine 300 mg once daily in the morning (n = 10) or previous evening (n = 18) or 150 mg twice daily (n = 11) as part of a combination therapy for HIV. Their exclusively breastfed infants were fed on demand and had blood samples taken at 2 and 8 hours after the dose. Lamivudine was detectable (>16.6 mcg/L) in the dried blood spots of 36% (14 of 39) of infants, at a median of

17.7 mcg/L (IQR 16.3 to 22.7 mcg/L). Of these, detectable levels were found in 7 of 10 (70%) infants whose mothers had 300 mg once daily in the morning, in 4 of 18 (22%) of those whose mothers had taken their dose the previous evening, and in 3 of 11 (27%) infants whose mothers were given the drug twice daily.[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]

Twenty-four infants who were breastfed by HIV-positive mothers developed HIV infection by 6 months of age. Six of these infants had a mutation that might have been selected for by subtherapeutic levels of lamivudine in breastmilk.[25]

An HIV-positive mother took a combination tablet containing dolutegravir 50 mg, abacavir sulfate 600 mg and lamivudine 300 mg (Triumeq) once daily. Her infant was exclusively breastfed for about 30 weeks and partially breastfed for about 20 weeks more. No obvious side effects were noted.[26]

One mother took lamivudine for 33 days, 25 before birth and eight days postpartum for chronic hepatitis B infection. Her infant was breastfed (extent not stated). At three months of age, the infant died with the death attributed to sudden infant death syndrome. The death was unlikely to be related to lamivudine.[27]

Effects on Lactation and Breastmilk

Some case reports and in vitro studies have suggested that protease inhibitors might cause hyperprolactinemia and galactorrhea in some male patients,[28][29] although this has been disputed.[30] One case series found an incidence of gynecomastia of 2.4 cases per person annually among men receiving highly active antiretroviral therapy; 51% of the affected patients were taking lamivudine. Gynecomastia was unilateral initially, but progressed to bilateral in 53% of cases. No alterations in serum prolactin were noted and spontaneous resolution usually occurred within one year, even with continuation of the regimen.[31] 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.

Alternate Drugs to Consider

(Hepatitis B) Interferon Alfa, Tenofovir

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Substance Identification

Substance Name

Lamivudine

CAS Registry Number

134678-17-4

Drug Class

Breast Feeding

Lactation

Anti-Infective Agents

Anti-HIV Agents

Antiviral Agents

Anti-Retroviral Agents

Reverse Transcriptase Inhibitors