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Lopinavir

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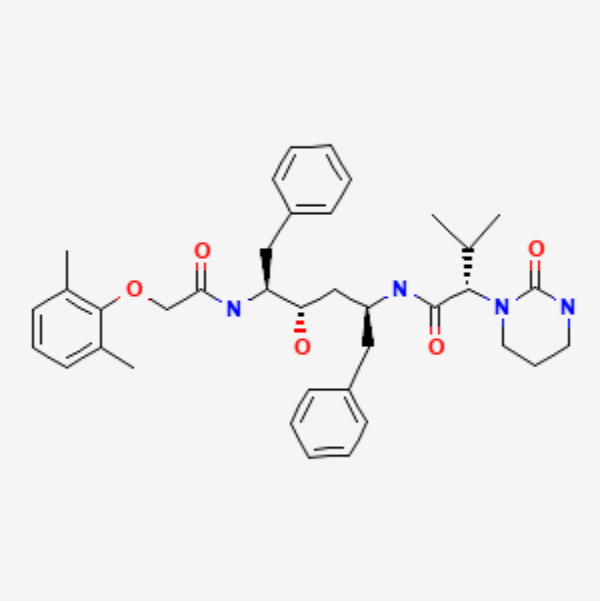

Drug Levels and Effects

Summary of Use during Lactation

Lopinavir appears in breastmilk in low levels and can be found in the serum of some breastfed infants. Although lopinavir has been associated with impaired adrenal gland function when given directly to infants, the effect is dose related.[1] No adverse infant effects have been clearly caused by the small amounts of lopinavir in breastmilk. 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.[2,3] Extended postnatal prophylaxis of breastfed infants with the lopinavir-ritonavir combination should continue until breastfeeding is stopped.[4]

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Ritonavir used as a booster has been studied in several studies of breastfeeding mothers. It is excreted into milk in measurable concentrations and low levels can be found in the blood of some breastfed infants. No reports of adverse reactions in breastfed infants have been reported. For more information, refer to the LactMed record on ritonavir.

Drug Levels

Maternal Levels. One study measured lopinavir in breastmilk samples from nursing mothers who had been randomized to receive the drug as part of a clinical trial to evaluate maternal to child transmission of HIV infection. The dosages, dosage regimens and time of breastmilk sample collection times were not reported. Lopinavir was not detected in any of 60 breastmilk samples.[5]

Nine mothers who were receiving lopinavir 400 mg plus ritonavir 100 mg twice daily as part of a combination antiretroviral regimen provided a total of 23 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 lopinavir concentration was 1834 mcg/L (range 557 to 3950 mcg/L).[6]

Fifteen women had been taking lopinavir 400 mg twice daily for 53 to 182 days as part of a drug combination that included ritonavir, zidovudine, and lamivudine. Breastmilk samples were collected at just before a dose at a median of 1 month postpartum. Whole breastmilk levels contained a median of 0.06 mg/L of lopinavir, which was a median of 0.7% of maternal blood levels.[7]

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 seventeen of the 121 breastmilk samples contained detectable quantities (10 mcg/L or greater) of lopinavir, with a median breastmilk concentration of 1.43 mg/L over the 6 hours.[8]

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 lopinavir was 4263 mcg/L (range 1143 to 5573 mcg/L).[9]

Mothers who were taking lopinavir 400 mg with ritonavir 100 mg twice daily hand-expressed breastmilk 1 to 2 hours after the morning dose at 1, 3 and 6 months postpartum. Median breastmilk lopinavir concentrations were 530 mcg/L (n = 6), 650 mcg/L (n = 8), 590 mcg/L (n = 8) at 1, 3 and 6 months, respectively. The weight-adjusted infant dosage was calculated to be 0.23% at 6 months.[10]

Infant Levels. Breastfed infants of 9 mothers who were receiving lopinavir 400 mg plus ritonavir 100 mg twice daily as part of a combination antiretroviral regimen had a total of 6 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 lopinavir plasma concentrations was 105 mcg/L (range 12 to 518 mcg/L), which was a median of 8% (range 0 to 16%) of the maternal serum concentration.[6]

Five infants were breastfed either partially or exclusively by their mothers who had been taking lopinavir 400 mg twice daily for 53 to 182 days as part of a drug combination that included ritonavir, zidovudine, and lamivudine. Infant blood was collected at a median of 1 month postpartum at 11 to 16 hours after the last dose and a median of 1 hour (range 6 minutes to 35 hours) after the last breastfeeding. Two of five infants had measurable lopinavir plasma levels of <1 mg/L.[7]

Lopinavir was measured in 117 breastfed (90% exclusive) infants whose mothers were taking lopinavir plus ritonavir for HIV infection during pregnancy and postpartum. At 8 weeks postpartum, only 2% had detectable lopinavir in their plasma at a mean concentration of 0.17 mg/L. At 12 weeks postpartum, none of the infants had detectable lopinavir in their plasma, and 96% of infants had detectable lopinavir in their hair samples at a mean concentration of 5.1 ng/mg of hair (range 0.13 to 15.8 ng/mg). The authors interpreted the results to mean that infants receive negligible exposure to lopinavir during breastfeeding.[11]

Thirty nursing mothers were studied at 6, 12 or 24 weeks postpartum (10 at each time). Each mother was taking lopinavir 400 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. Lopinavir was undetectable (<10 mcg/L) in all of the 115 infant plasma samples.[8]

Mother-infant pairs were studied among mothers taking lopinavir 400 mg with ritonavir 100 mg twice daily as part of a multi-drug HIV regimen. Infants were breastfed (extent not stated) and plasma concentrations were measured postpartum. Median plasma lopinavir concentrations at 1 (n = 3), 3 (n = 9), and 6 months (n = 8) were all less than the lower limit of quantification of 264 mcg/L. Only 2 samples had measurable lopinavir.[10]

Effects in Breastfed Infants

A study compared the rates of severe anemia in 3 groups of infants who received postpartum prophylaxis with zidovudine for prevention of maternal-to-child transmission of HIV infection. Through 6 months of age, breastfed infants whose mothers received HAART had a higher rate of severe anemia (7.4%) than breastfed infants whose mothers received only zidovudine (5.3%). Formula-fed infants had the lowest rate of severe anemia (2.5%). The anemia generally responded well to iron and multivitamin supplementation, and discontinuation of zidovudine.[12]

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.[13]

Among 9 breastfed (extent not stated) infants whose mothers were taking lopinavir 400 mg with ritonavir 100 mg twice 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.[10]

Effects on Lactation and Breastmilk

Gynecomastia has been reported among men receiving highly active antiretroviral therapy. Gynecomastia is unilateral initially, but progresses to bilateral in about half of cases. No alterations in serum prolactin were noted and spontaneous resolution usually occurred within one year, even with continuation of the regimen.[14-16] Some case reports and in vitro studies have suggested that protease inhibitors might cause hyperprolactinemia and galactorrhea in some male patients,[17,18] although this has been disputed.[19] 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

Lopinavir

CAS Registry Number

192725-17-0

Drug Class

Breast Feeding

Lactation

Milk, Human

Anti-Infective Agents

Antiviral Agents

Anti-HIV Agents

Anti-Retroviral Agents

HIV Protease Inhibitors