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Ritonavir

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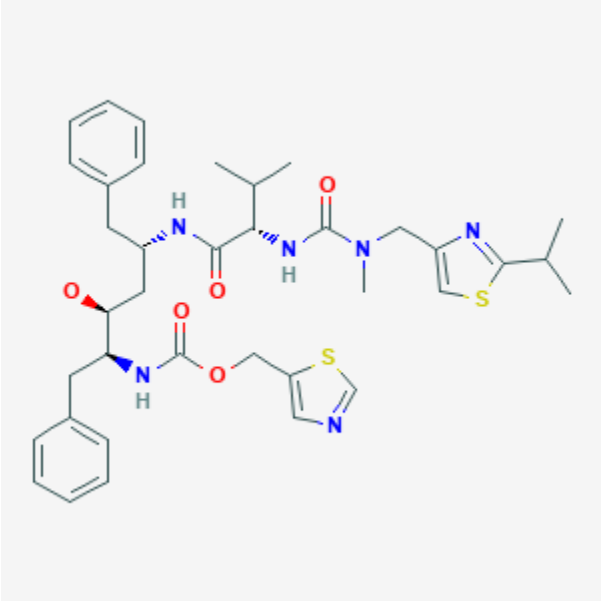

Drug Levels and Effects

Summary of Use during Lactation

In the United States and other developed countries, HIV-infected mothers should generally not breastfeed their infants. Published experience with ritonavir during breastfeeding is limited. 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.[1] 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.[2][3]

Hepatitis C is not transmitted through breastmilk[4][5] and breastmilk has been shown to inactivate hepatitis C virus (HCV).[6][7] However, the Centers for Disease Control recommends that mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding. It is not clear if this warning would apply to mothers who are being treated for hepatitis C. Infants born to mothers with HCV infection should be tested for HCV infection; because maternal antibody is present for the first 18 months of life and before the infant mounts an immunologic response, nucleic acid testing is recommended.[4][5]

Drug Levels

Maternal Levels. One study measured ritonavir 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 times of breastmilk sample collection times were not reported. Ritonavir was not detected in any of 60 breastmilk samples.[8]

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 ritonavir concentration was 79 mcg/L (range 31 to 193 mcg/L).[9]

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 twelve of the 121 breastmilk samples contained detectable quantities (10 mcg/L or greater) of ritonavir, with a median breastmilk concentration of 79 mcg/L over the 6 hours.[10]

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 ritonavir was 240 mcg/L (range 98 to 402 mcg/L).[11]

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 ritonavir plasma concentration was 7 mcg/L (range 0 to 138 mcg/L), which was a median of 12% (range 11 to 40%) of the maternal serum concentration.[9]

Ritonavir was measured in 117 breastfed (90% exclusive) infants whose mothers were taking lopinavir plus ritonavir for HIV infection during pregnancy and postpartum. At 8 and 12 weeks postpartum, none of the infants had detectable ritonavir in their plasma; 91% of infants had detectable ritonavir in their hair samples at 12 weeks postpartum at a mean concentration of 0.15 ng/mg of hair (range 0.03 to 0.42 ng/mg). The authors interpreted the results to mean that infants receive negligible exposure to ritonavir during breastfeeding.[12]

Thirty nursing mothers were studied at 6, 12 or 24 weeks postpartum (10 at each time). Each mother was taking ritonavir 100 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. Ritonavir was undetectable (<10 mcg/L) in all of the 115 infant plasma samples.[10]

Effects in Breastfed Infants

Relevant published information was not found as of the revision date.

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.[13][14][15] Some case reports and in vitro studies have suggested that protease inhibitors might cause hyperprolactinemia and galactorrhea in some male patients,[16][17] although this has been disputed.[18] 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

Ritonavir

CAS Registry Number

155213-67-5

Drug Class

Breast Feeding

Lactation

Anti-Infective Agents

Anti-HIV Agents

Antiviral Agents

Anti-Retroviral Agents

HIV Protease Inhibitors