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Tacrolimus

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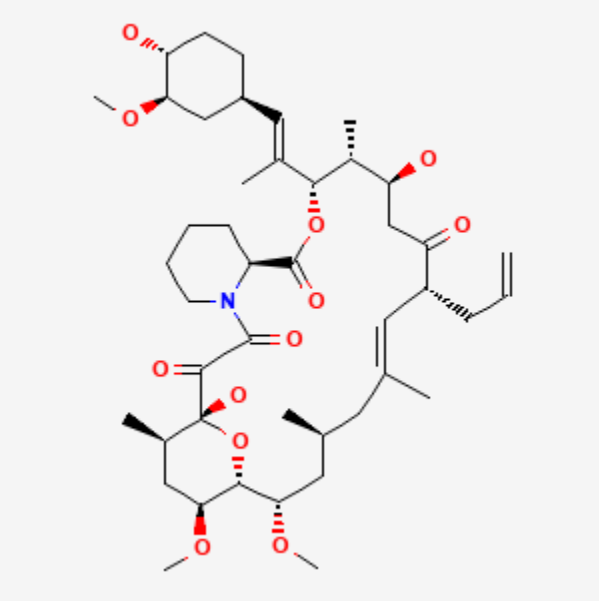

Drug Levels and Effects

Summary of Use during Lactation

Limited data indicate that amounts of systemically administered tacrolimus are low in breastmilk and probably do not adversely affect the breastfed infant. United States and European experts and guidelines consider tacrolimus to be probably safe to use during breastfeeding.[1-9] Exclusively breastfed infants should be monitored if this drug is used during lactation, possibly including measurement of serum levels to rule out toxicity if there is a concern.

Topical tacrolimus presents a low risk to the nursing infant because it is poorly absorbed after topical application and peak blood concentrations are less than 2 mcg/L in most patients. Ensure that the infant's skin does not come into direct contact with the areas of skin that have been treated. Current guidelines allow topical

tacrolimus to be applied to the nipples just after nursing, with the nipples cleaned gently before nursing.[10,11] Only water-miscible cream or gel products should be applied to the breast or nipple because ointments may expose the infant to high levels of mineral paraffins via licking,[5] so pimecrolimus cream may be preferable to tacrolimus ointment for nipple application.

Drug Levels

Maternal Levels. Random tacrolimus colostrum levels in 10 samples from 6 mothers averaged 1.7 mcg/L (range 0.3 to 1.9 mcg/L) which was about 50% of maternal serum levels. Tacrolimus dosages in these mothers were not reported.[12]

One mother taking 3 mg twice daily (0.1 mg/kg per day), had a peak milk level of 0.57 mcg/L one hour after the dose. The half-life in milk was estimated to be 12.85 hours. The authors estimated that her breastfed infant would receive 0.06% of the maternal weight-adjusted dosage or 0.06 mcg/kg daily, which is 0.03 to 0.04% of the oral starting dosage for pediatric patients.[13]

One mother who had been taking tacrolimus for a kidney transplant 5 years earlier was 3 months postpartum and exclusively breastfeeding her infant. She had been taking a dosage of 2 mg orally twice daily (0.05 mg/kg per day) for at least 2 months. She was also taking atenolol 100 mg, azathioprine 100 mg, diltiazem 180 mg, furosemide 20 mg, and prednisone 5 mg daily. Milk samples obtained over a 12-hour dosage interval found little change throughout the day, with the highest levels of 2.1 mcg/L at 4 and 8.5 hours after the dose. The average milk concentration was 1.8 mcg/L. The authors calculated that an exclusively breastfed infant would receive a daily dosage of 0.27 mcg/kg which is about 0.5% of the maternal weight-adjusted dosage and less than 0.2% of the pediatric dosage for organ transplant rejection.[14]

Eleven women who took tacrolimus (exact dosages not specified, but assumed to be 6 mg daily) during pregnancy and postpartum donated 22 breastmilk samples (times unspecified) for analysis. The median breastmilk concentration was 0.8 mcg/L (range 0.1 to 1.6 mcg/L). Two women took samples before and 4 or more hours after a dose; no difference in milk levels was seen. The authors estimated that the maximum dosage that an exclusively breastfed infant would receive would be 0.56 mcg daily, equivalent to 0.23% of the maternal weight-adjusted dosage. Additionally, comparing infants who were breastfed to those who were not, the serum tacrolimus concentrations fell at about the same rate over the first 2 weeks postpartum, regardless of breastfeeding status, indicating that breastfeeding did not prolong infant tacrolimus levels.[15]

Eleven breastmilk samples were obtained via breast pump over a 12-hour dosage interval in a nursing mother who was 45 weeks postpartum and receiving tacrolimus 1.5 mg twice daily after a liver transplant. The peak tacrolimus milk level of 1.11 mcg/L occurred 6 hours after the dose. The average tacrolimus level in milk was 0.93 mcg/L. The milk concentration of the active metabolite, 13-demethyltacrolimus, averaged 0.03 mcg/L (range 0.01 to 0.04 mcg/L). The authors estimated that a fully breastfed infant would receive 0.14 mcg/kg daily or 0.3% of the maternal weight-adjusted dosage.[3]

Fourteen mothers with organ transplants donated 5 colostrum samples on day 2, 3 or 4 postpartum before a dose, and 2, 4, 6 and 8 hours after a dose of tacrolimus. Tacrolimus dosages ranged from 4 to 14 mg daily in 2 divided doses and were adjusted to attain maternal serum levels between 5 and 10 mcg/L. The highest colostrum levels were seen at 8 hours after the dose and averaged 3.2 mcg/L for tacrolimus, 0.56 mcg/L for 13-O-desmethyltacrolimus. The metabolite 15-O-desmethyltacrolimus reached its highest mean colostrum levels of 0.29 mcg/L at 6 hours after the dose. The metabolite 31-O-desmethyltacrolimus was not detectable in colostrum. None of the infants were breastfed, but the mean daily dosages calculated to be ingested by the breastfed infants were 151.4 ng/kg of tacrolimus, 23.80 ng/kg for 13-O-desmethyltacrolimus, and 13.25 for 15-O-desmethyltacrolimus.[16]

Thirteen Japanese women with systemic lupus erythematosus were treated with an average tacrolimus dose of 3.2 mg (range 2 to 5.5 mg) once daily. Milk samples were obtained immediately prior to a dose, and 2 and 12 hours after the dose. Median levels were 3 mcg/L for the trough, 3.8 mcg/L at 2 hours, and 3.7 mcg/L at 12 hours. The median weight-adjusted percent of maternal dosage was reportedly 0.18% (range 0.12 to 0.35%), although the exact method of calculation was not clearly specified.[17] Note that the data table and the text disagree on units of measurement. This paper would only be consistent with other papers if units were in ng/mL (mcg/L).

A woman was taking tacrolimus 1.5 mg twice daily during pregnancy and postpartum. Four days after delivery, her milk tacrolimus level was 1.1 mcg/L at an unspecified time after the dose. On day 21 postpartum, milk levels were 1.4 mcg/L at the time of the morning dose, 1.3 mcg/L at 4 hours after the dose, 1.6 mcg/L at 8 hours after the dose, and 1.4 mcg/L at 12 hours after the dose. The authors estimated that a fully breastfed infant would receive 0.4% of the mother's weight-adjusted dosage.[18]

Infant Levels. Four breastfed (3 exclusive, 1 partial) infants whose mothers took tacrolimus during breastfeeding had serum tacrolimus concentrations measured between day 15 and 27 of age. The mothers' mean daily tacrolimus dosage during breastfeeding was 9.6 mg daily (range 4.5 to 15 mg daily). Tacrolimus was undetectable (<1.9 mcg/L) in all of the infants.[19]

A woman was taking tacrolimus 6 mg twice daily during pregnancy to prevent rejection of a small intestine transplant. Her dosage was adjusted to maintain an optimal tacrolimus blood level postpartum, although the exact dosage was not stated. She breastfed (extent not stated) her infant and at 1 week of age, the infant's tacrolimus blood level was less than 1 mcg/L.[20]

Twelve infants were exclusively breastfed by mothers taking tacrolimus (exact dosages not specified) during pregnancy and postpartum. Twenty-four infant blood samples were obtained from the infants at various times. The median infant blood tacrolimus concentration was 1.3 mcg/L (range 0.0 to 4.0 mcg/L). In infants in whom serial blood levels were obtained, levels declined at about 15% daily. Blood tacrolimus levels in breastfed infants were no higher than those in 3 additional infants who were not breastfed. Eight breast-fed infants with serial blood samples had undetectable (<0.1 mcg/L) tacrolimus blood levels at a median of day 14 (interquartile range day 11 to 22) postpartum.[15]

Two mothers with systemic lupus erythematosus were reported who have taken tacrolimus during pregnancy and lactation. One took tacrolimus 3 mg and prednisolone 40 mg daily and the other took tacrolimus 3 mg and prednisolone 30 mg daily during breastfeeding. The infants' blood tacrolimus levels measured 1 hour after breastfeeding were 0.2 mcg/L in the first infant at 10 days of age, and 0.5 mcg/L in the second at 7 days of age.[21]

Thirteen infants were breastfed (extent not stated) by mothers with systemic lupus erythematosus and were treated with an average tacrolimus dose of 3.2 mg (range 2 to 5.5 mg) once daily. Infant blood samples were obtained 2 to 4 hours after a maternal dose at 1 to 3 months of age, but the time of the prior breastfeeding was not stated. All infants had undetectable (lower limit of detection not stated) blood tacrolimus levels.[17]

A woman was taking tacrolimus 1.5 mg twice daily during pregnancy and postpartum. Immediately after delivery (7 hours after the prior dose), the infant's blood tacrolimus concentration was 3 mcg/L. The infant was in the neonatal ICU and fed 40 to 80 mL of breastmilk and 420 to 500 mL of formula daily. On day 4 of life, the infant's blood tacrolimus concentration was 1.5 mcg/L; on day 21 postpartum, tacrolimus was undetectable (<0.5 mcg/L) in in the infant's blood.[18]

Effects in Breastfed Infants

One infant was exclusively breastfed during maternal tacrolimus therapy throughout gestation to at least 2.5 months of age at which time the infant was developing normally physically and neurologically. An ultrasound examination of the infant's thymus was normal.[13]

The National Transplantation Pregnancy Registry reported data gathered from 1991 to 2011 on mothers who breastfed their infants following organ transplantation. A total of 68 mothers with transplants (mostly kidney or liver) used tacrolimus while breastfeeding a total of 83 infants. Duration of nursing ranged from 1 week to 1.5 years and follow-up of the children ranged from weeks to 16 years. There were no reports of problems in any of the infants or children.[5] As of December 2013, a total of 92 mothers had breastfed 125 infants for as long as 26 months with no apparent adverse effects in infants.[6]

The breastfed infants of six women who took tacrolimus during pregnancy for organ transplantation were breastfed (4 exclusive, 2 partial) for 45 to 180 days and followed for periods of 2 to 30 months. The mothers' mean daily tacrolimus dosage during breastfeeding was 9.6 mg daily (range 4.5 to 15 mg daily). Four mothers were also taking azathioprine 100 to 150 mg daily, one was taking diltiazem, and one was taking prednisolone 15 mg and aspirin 75 mg daily. None of the infants had any clear tacrolimus-related side effects, although one had transient thrombocytosis that resolved despite continued breastfeeding. Developmental milestones were normal and no pattern of infections was noted.[19]

Two mothers with systemic lupus erythematosus were reported who took tacrolimus 3 mg daily during pregnancy and lactation as well as prednisolone 30 or 40 mg daily. Three years after birth, both children were healthy. The durations of lactation were not stated.[21]

In a case series of women who had liver transplants over a 25-year period, one woman breastfed (extent not stated) her infant while taking tacrolimus. No neonatal complications were noted.[22]

A mother with a liver transplant was maintained on belatacept 10 mg/kg monthly, slow-release tacrolimus (Envarsus and Veloxis) 2 mg daily, azathioprine 25 mg daily, and prednisone 2.5 mg daily. She breastfed her infant for a year (extent not stated). The infant's growth and cognitive milestones were normal.[23]

An Australian case series reported 3 women with heart transplants who had a total of 5 infants, all of whom were breastfed (extent not stated) during maternal tacrolimus therapy. Daily dosages ranged from 3 to 13 mg daily. No adverse infant effects were reported up to the times of discharge.[24]

A woman with rheumatoid arthritis refractory to etanercept took sarilumab 200 mg every two weeks during pregnancy until 37 weeks of gestation. She was also taking prednisolone 10 mg and tacrolimus 3 mg daily. She delivered a healthy infant at 38 weeks of gestation and breastfed her infant. Prednisolone was continued postpartum, tacrolimus was restarted at 7 days postpartum, and sarilumab was restarted at 28 days postpartum. The mother continued to breastfeed until 6 months postpartum. The infant was vaccinated with multiple live vaccines after reaching six months old, including the Bacille-Calmette-Guerin vaccine, with no adverse effects.[25]

Effects on Lactation and Breastmilk

A study in renal transplant patients who were on a tacrolimus-based immunosuppression regimen found that women's median serum prolactin levels were 14.4 mcg/L compared with women who were not taking tacrolimus (17.6 mcg/L). The difference was statistically significant. Median serum testosterone levels (0.121 vs 0.137 mcg/L) and serum cortisol levels (82.5 vs 105 mg/L) were also significantly lower in the tacrolimus group.[26] The reduced prolactin may be caused by inhibition of the transcription of the human prolactin gene.[27] Not all studies have found a reduction in serum prolactin with tacrolimus.[28] The prolactin level in a mother with established lactation may not affect her ability to breastfeed.

Alternate Drugs to Consider

(Transplantation) Azathioprine, Cyclosporine; (Topical) Pimecrolimus

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Substance Identification

Substance Name

Tacrolimus

CAS Registry Number

104987-11-3

Drug Class

Breast Feeding

Lactation

Milk, Human

Immunosuppressive Agents

Dermatologic Agents