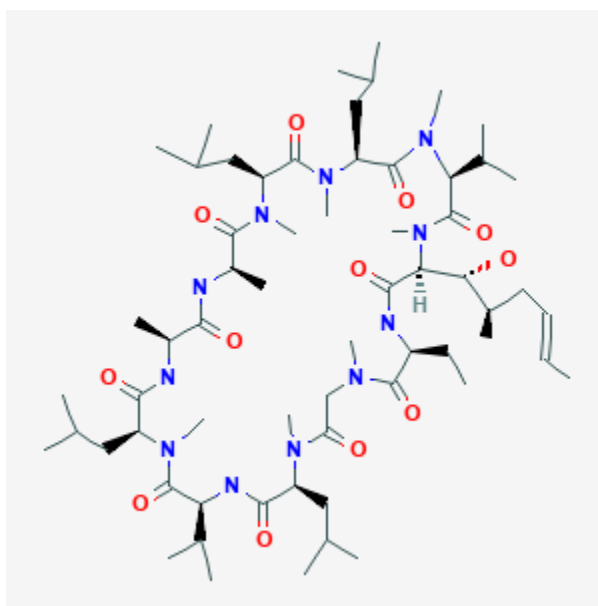




Cyclosporine

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Drug Levels and Effects

Summary of Use during Lactation

Cyclosporine concentration in milk is variable. With typical maternal cyclosporine blood levels, a completely breastfed infant would usually receive no more than about 2% of the mother's weight-adjusted dosage or pediatric transplantation maintenance dosage, and often less than 1%. Most infants studied have not had detectable cyclosporine blood levels, but 2 infants have had measurable levels, 1 with blood levels in the therapeutic range despite relatively low maternal milk levels.

Numerous infants have been breastfed during maternal cyclosporine use, usually with a concurrent corticosteroid and sometimes with concurrent azathioprine. At least 2 mothers successfully breastfed a second infant after successfully breastfeeding the first infant. No reports of adverse effects on infants growth, development or kidney function have been reported, although thorough follow-up examinations have not always been performed or reported. Some reviewers believe breastfeeding should be discouraged during cyclosporine

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use, but these opinions appear to be based on limited, early data.[1][2] European experts, the National Transplantation Pregnancy Registry and other experts consider cyclosporine to be probably safe to use for inflammatory bowel disease during breastfeeding,[3][4][5][6][7] although others have expressed concern.[8] 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.

Because absorption from the eye is limited, ophthalmic cyclosporine would not be expected to cause any adverse effects in breastfed infants. To substantially diminish the amount of drug that reaches the breastmilk after using eye drops, place pressure over the tear duct by the corner of the eye for 1 minute or more, then remove the excess solution with an absorbent tissue.

Drug Levels

Maternal Levels. Early reports measured cyclosporine in breastmilk unsystematically. Cyclosporine levels of 101, 109 and 263 mcg/L were detected in random samples of breastmilk on days 2, 3 and 4 postpartum from a woman taking 450 mg daily orally.[9] In one woman, a single milk concentration of 16 mcg/L was measured 22 hours after an oral dose of 325 mg given 2 hours before the onset of labor.[10] One mother's cyclosporine milk concentration averaged about 17% (range 12 to 22%) of simultaneous serum levels.[11] In another mother, milk cyclosporine levels ranged from 15 to 90% higher than simultaneous serum levels. However, the authors estimated that a breastfed infant would receive less than 5% of an immunosuppressive dose.[12] One breastfed infant was estimated to have a daily cyclosporine intake of 6 mcg/kg daily during maternal use of 225 mg daily of cyclosporine.[13]

A case series of 3 mothers found the following cyclosporine levels in colostrum. The first mother was receiving 200 mg every 12 hours and had a colostrum level of 418 mcg/L 12 hours her last predelivery dose. The second mother was taking 150 mg every 12 hours and had a mean of 99 mcg/L (range 36 to 209 mcg/L) in 5 colostrum samples taken 3 to 5 days after delivery; The third mother was taking a dose of 125 mg every 12 hours and had levels of 45 to 83 mcg/L in 7 colostrum samples taken during the first 4 days postpartum; milk levels were 105 to 203 mcg/L in samples taken during days 6 to 10 postpartum.[14]

A mother taking 3 mg/kg twice daily with a blood trough cyclosporine blood level of 260 mcg/L had average milk levels of 596 mcg/L 5 weeks postpartum with milk levels varying with the time after the dose. The authors estimated that a fully breastfed infant would receive less than 0.1 mg/kg daily or less than 1.7% of the maternal weight-adjusted dosage.[15]

Five mothers taking cyclosporine in unspecified dosages had random milk levels ranging from 50 to 227 mcg/L in the immediate postpartum period. Two of these women collected several milk samples over the course of a day. A mother with a trough cyclosporine blood level of 62 mcg/L had milk levels ranging from 25 to 120 mcg/L. The other mother with a trough blood level of 110 mcg/L had milk levels ranging from 87 to 440 mcg/L. The authors estimated that a fully breastfed infant would receive less than 300 mcg of cyclosporine daily.[16]

One mother taking cyclosporine 300 mg twice daily had serum levels of 123 to 273 mcg/L and milk levels ranging from 79 to 286 mcg/L on 3 occasions over a 10-week period.[17]

Variable milk levels of cyclosporine were noted in a case series of 5 mother-infant pairs. Individual average milk cyclosporine levels varied from 98 to 118 mcg/L (range 45 to 203 mcg/L) in 3 of the mothers. A fourth mother taking a dose of 5.3 mg/kg daily of Neoral had mean foremilk levels of 465 mcg/L and hindmilk levels of 564 mcg/L (minimum foremilk 158 mcg/L, maximum hindmilk 1016 mcg/L). Estimated intake for the 5 infants averaged 0.86% (range from 0.2 to 2.1%) of the maternal weight-adjusted dosage. In 3 of the infants, calculated intake averaged 0.05 mg/kg (range 0.01 to 0.08 mg/kg) daily or about 1% of the pediatric maintenance dosage. [18]

A woman was taking oral cyclosporine 100 mg in the morning and 75 mg in the evening (2.1 mg/kg daily) during pregnancy and lactation. She was also taking azathioprine 75 mg and prednisone 10 mg daily. A milk sample was obtained 2 hours after the mother's morning dose. The breastmilk cyclosporine concentration was 46 mcg/L.[19]

A woman was taking cyclosporine for severe psoriasis during late pregnancy and while nursing. While taking a dose of 200 mg daily (apparently 100 mg twice daily), she collected milk samples 2 hours after her morning dose on 3 occasions. Milk cyclosporine levels were 128 mcg/L on day 10, 200 mcg/L on day 30, and 364 mcg/L on day 50. On day 40, the milk cyclosporine concentration before her morning dose was 207 mcg/L.[20]

A woman was receiving cyclosporine 1.5 mg/kg daily and everolimus 2 mg/kg daily during pregnancy and postpartum following a heart transplant. A colostrum sample was obtained one day postpartum which contained a cyclosporine level of 15.5 mcg/L. The timing of the sample with respect to the previous cyclosporine dose was not stated.[21]

Infant Levels. In 7 mothers who breastfed their infants during cyclosporine use (dosages not stated), infant serum cyclosporine levels were undetectable (<30 mcg/L).[16] Another exclusively breastfed infant reportedly had undetectable serum cyclosporine levels (<25 mcg/L) with a maternal dose of 300 mg twice daily of the microemulsion.[17] A partially breastfed infant whose mother was taking 125 mg twice daily had cyclosporine blood levels of 18 to 21 mcg/L during the first 21 days of life.[14] Another mother taking cyclosporine 3 mg/kg twice daily exclusively breastfed her daughter who had undetectable (<3 mcg/L) cyclosporine blood levels.[10] Among 4 infants in whom blood levels were measured, 3 had undetectable levels, but the fourth had "therapeutic" blood levels of 117 and 131 mcg/L on 2 occasions even though the infant's estimated dosage was only 1.1% of maternal weight-adjusted dosage.[18]

A 6-day-old infant who was about 50% breastfed had an undetectable (<10 mcg/L) cyclosporine whole blood concentration. The infant's mother was taking oral cyclosporine 100 mg in the morning and 75 mg in the evening (2.1 mg/kg daily) during pregnancy and lactation. The authors estimated that the cyclosporine dose this infant would receive if it were fully breastfed was 0.007 mg/kg or 0.33% of the weight-adjusted maternal dose. [19]

Two cases were reported of infants whose mothers were taking cyclosporine and breastfeeding. One mother was taking cyclosporine 200 mg daily as well as azathioprine, prednisone, diltiazem and folate. She exclusively breastfed her infant and at 1 week postpartum the infant's serum had undetectable (<15 mcg/L) cyclosporine levels while the mother's serum contained 68 mcg/L. The second mother was taking cyclosporine 120 mg daily as well as methyldopa, prednisone, and calcitriol. She exclusively breastfed her infant and at 2 weeks postpartum the infant's serum had undetectable (<15 mcg/L) cyclosporine levels while the mother's serum contained 39 mcg/L.[22]

A woman with severe ulcerative colitis during pregnancy received cyclosporine 5 mg/kg daily from 26 weeks of pregnancy and continued while breastfeeding. She extensively breastfed her infant and the infant's serum cyclosporine concentrations after the morning feed were consistently undetectable (<30 mcg/L).[23]

An infant whose mother took cyclosporine 200 mg daily for severe psoriasis during late pregnancy and while nursing. The infant was exclusively breastfed for 6 months. The infant's cyclosporine blood levels were 30 mcg/L on day 10 at 2 hours after the maternal dose, and undetectable (<25 mcg/L) on days 30, 40 and 50. The authors hypothesized that the level reported on day 10 derived from cyclosporine in the infant's adipose tissue, received during pregnancy.[20]

In summary, reported milk cyclosporine levels vary considerably in several case reports and series. This variability seems to be partially due to inconsistent sampling times among the reports and probably related to the fat content of the milk at the time of sampling. In one patient, cyclosporine levels averaged 21% higher in the

high-fat hindmilk than in the low-fat foremilk.[18] In another patient, milk levels increased from the first few days of colostrum to the later mature milk phase. Estimations of the total amounts of drug in milk received by the infant are less than 5% of the maternal weight-adjusted dose, and as low as 0.01% in some infants. This translates to less than 2% of the pediatric transplantation maintenance dosage of cyclosporine in most infants. In most breastfed infants, cyclosporine is not detectable in blood; however, occasionally infants have had detectable blood levels, even when milk levels and infant dosage were apparently low.[10][14][18]

Effects in Breastfed Infants

One infant was breastfed and follow-up showed that the infant remained healthy and normal.[13]

A mother who was taking cyclosporine 3 mg/kg twice daily completely breastfed her infant until weaning with partial breastfeeding until 14 months. The infant's kidney function was stable and she was healthy at 2 years of age. This mother also breastfed a second infant.[15]

In 7 infants breastfed for 4 to 12 months during maternal cyclosporine and prednisolone (plus azathioprine in 6 of the 7), infant renal function was unaffected, and they grew normally.[16]

One mother partially breastfed her infant during cyclosporine, azathioprine and prednisone use. No follow-up data were reported.[14]

One infant was exclusively breastfed for 10.5 months during maternal use of cyclosporine 300 mg twice daily, azathioprine and prednisone. Partial breastfeeding continued for 2 years. The infant thrived with normal growth at 12 months. The mother also breastfed a second child while on the same drug regimen.[17]

Four infants breastfed during maternal cyclosporine use. In three, no adverse effects were noted clinically on follow-up and one of these had normal serum creatinine and urea nitrogen (BUN) measured. No follow-up was reported on the fourth infant.[18]

Two cases were reported of infants whose mothers were taking cyclosporine and breastfeeding. One mother was taking cyclosporine 200 mg daily as well as azathioprine, prednisone, diltiazem, and folate. The second mother was taking cyclosporine 120 mg daily as well as methyldopa, prednisone, and calcitriol. Both mothers exclusively breastfed their infants initially and continued for 5 and 14 months, respectively. The infants were reportedly healthy and had normal renal function.[22]

A woman with severe ulcerative colitis during pregnancy received cyclosporine 5 mg/kg daily from 26 weeks of pregnancy and continued while breastfeeding. She extensively breastfed her infant and at 3 months of age the infant was healthy.[23]

The National Transplantation Pregnancy Registry reported data gathered from 1991 to 2011 on mothers who breastfed their infants following organ transplantation. A total of 43 mothers with transplants (mostly kidney) used cyclosporine while breastfeeding a total of 49 infants. Duration of nursing ranged from 1 week to 2 years and follow-up of the children ranged from weeks to 16 years. One infant experienced mildly elevated platelet count and an abnormal albumin/globulin ratio for age; at 16 months, laboratory values were normal. There were no reports of problems in the remainder of the infants or children.[4] As of December 2013, a total of 43 mothers had breastfed 55 infants for as long as 24 months with no apparent adverse effects in infants.[5]

A woman took cyclosporine 200 mg daily for psoriasis while exclusively breastfeeding her infant for 6 months. At 12 months of age, the infant was developing normally and had no discernible adverse effects from the drug in milk.[20]

Effects on Lactation and Breastmilk

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

Alternate Drugs to Consider

Azathioprine, Tacrolimus

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Substance Identification

Substance Name

Cyclosporine

CAS Registry Number

59865-13-3

Drug Class

Breast Feeding

Lactation

Immunosuppressive Agents