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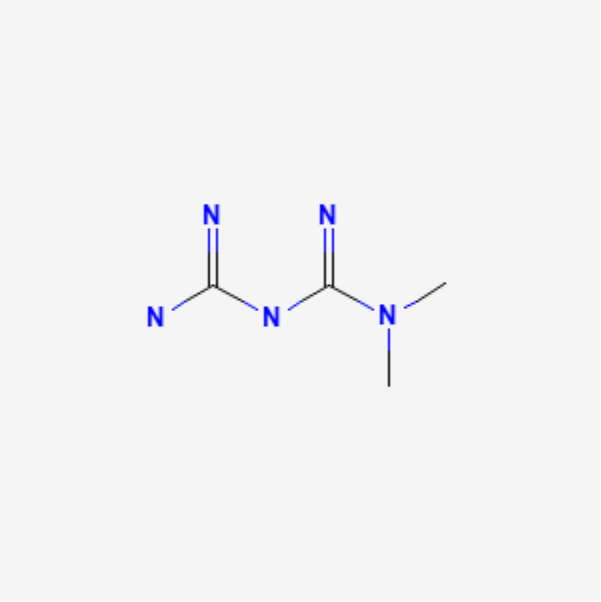
NLM Citation: Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Metformin. [Updated 2023 Oct 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Metformin

Revised: October 15, 2023.

CASRN: 657-24-9



Drug Levels and Effects

Summary of Use during Lactation

Data from well-conducted studies indicate that metformin levels in milk are low and infants would receive less than 0.5% of their mother's weight-adjusted dosage. Milk metformin levels are relatively constant during maternal metformin use, so timing of breastfeeding with respect to the administration times is of little benefit. Although the dose in milk is low, metformin is sometimes detectable in low levels in the serum of breastfed infants. One sizeable prospective study found no adverse effects in breastfed infants. Metformin is sometimes used as a galactogogue in women with reduced milk supply, but there is no evidence that it is effective. Metformin should be used with caution while nursing newborn and premature infants and those with renal impairment.

Drug Levels

Maternal Levels. Seven women (time postpartum not stated) were taking metformin with a median dose of 1500 mg daily (14 mg/kg daily; range 6.9 to 20 mg/kg daily) orally. Six of the women were taking an immediate-release product 500 mg three times daily and one was taking 500 mg as a sustained-release product once daily. Six women had milk levels that varied little over 24 hours and averaged 270 mcg/L. One woman had a slight rise in the milk level to about 380 mcg/L at about 4 to 5 hours after the dose. The authors estimated that an exclusively breastfed infant would receive an average daily dosage of 0.04 mg/kg (range 0.02 to 0.06 mg/kg) or 0.28% (range 0.16 to 0.4%) of the maternal weight-adjusted dosage with this maternal dosage regimen.[1,2]

Two lactating women who were 14 and 14.5 months postpartum took a single dose of 500 mg of immediate-release metformin. Milk levels were relatively constant over the next 72 hours with average levels of 130 and 270 mcg/L; a slight peak occurred in one mother 12 hours after the dose. The authors estimated that their infants received 0.11 and 0.25% of the maternal weight-adjusted dosage. Three other mothers were studied in the same way for 12 or 24 hours and had results consistent with the 2 more completely studied mothers.[3]

In the same paper, 3 women who had been taking immediate-release metformin 500 mg twice daily orally for at least several days were studied. Relatively stable milk levels averaging 130 to 270 mcg/L in the 3 mothers was found. The authors estimated that an exclusively breastfed infant would receive an average daily dosage of 29 mcg/kg (range 20 to 41 mcg/kg) or 0.2% (range 0.18 to 0.21%) of their mother's weight-adjusted dosage with this dosage regimen.[3]

Five women began metformin 500 mg twice daily on the first day postpartum. Trough and peak (2 hours after the dose) milk levels were collected 4 to 17 days postpartum. The average milk metformin levels were estimated to be 410 mcg/L. The authors estimated that an exclusively breastfed infant would receive an average of 0.65% of the maternal weight-adjusted dosage.[4]

Four women who were taking metformin during pregnancy and lactation provided breastmilk samples at 2- to 3-hour intervals over one dosage interval using a breast pump and emptying both breasts at each sampling time. The total amount of metformin excreted into milk was 0.13 mg with 1.5 grams daily (n = 1) and an average of 0.21 mg with 2 grams daily (n = 3). These values corresponded to daily infant dosages ranging from 0.024 to 0.050 mg/kg and an average of 0.25% (range 0.14 to 0.43%) of the weight-adjusted maternal dosage.[5]

Infant Levels. Serum levels were measured in 4 breastfed infants (ages and extent of nursing not stated) whose mothers were taking a median metformin dosage of 1.5 grams daily. In 2, metformin was undetectable (<10 mcg/L) 2.5 hours after the maternal dose, while in the other 2, levels of 50 and 80 mcg/L (10 and 15% of their mother's serum levels) were found at 6 and 5.3 hours after the maternal dose, respectively.[1,2]

Three women 2, 5 and 14 months postpartum who had been taking immediate-release metformin 500 mg twice daily orally for at least several days were studied. Metformin was undetectable (<5 mcg/L) in the serum of the 2 infants (extent of nursing not stated) aged 2 and 14 months in whom it was measured.[2]

Effects in Breastfed Infants

Seven infants aged 5 to 25 months whose mothers were taking metformin (start date and duration not stated) were judged to be healthy with growth and development progressing as expected. Two of the infants also had normal Denver Developmental Screening tests.[1]

Three infants aged 2, 5 and 14 months whose mothers were taking metformin 500 mg twice daily had no detectable adverse effects from metformin.[3]

In 3 breastfed (extent not stated) infants aged 10 to 11 days postpartum whose mothers were taking an average metformin dosage of 9.6 mg/kg (range 7.5 to 12.4 mg/kg) daily, none of the infants had low blood glucose levels. Their mothers reported no adverse reactions in the infants.[4]

Ninety-two mothers of 111 infants were treated with metformin in a mean dosage of 2.2 grams daily (range 1.5 to 2.55 mg daily) throughout pregnancy and postpartum. A 6-month, nonrandomized, prospective trial followed 61 predominantly breastfed and 50 formula-fed infants of these women. No differences in 3- and 6-month outcomes were found by blinded observers between the 2 groups of infants in height, weight, motor-social development or rates of illness.[6,7]

Effects on Lactation and Breastmilk

In a retrospective study of 250 women who received metformin 500 mg to 2 grams daily in either the immediate- or extended-release formulation for polycystic ovary syndrome, information on breastfeeding was available on 164 women. Of these, 97 (59%) were successful at breastfeeding, 27 (17%) failed, and 40 (27%) made no attempt to breastfeed. Of the 124 who attempted to breastfeed, 78% were successful. Failures were attributed to poor milk production in 4 women, demands of multiple births, infant prematurity, cleft palate and mastitis. Most of the women stopped metformin by the 12^{th} week of pregnancy.[8]

In a follow-up to a placebo-controlled study on metformin use during pregnancy in women with polycystic ovary syndrome, women were asked about the duration and extent of breastfeeding. No difference in breastfeeding in the duration of exclusive or partial breastfeeding was observed between the women who received metformin during pregnancy and those who received placebo.[9]

A small pilot study of women with low milk supply and at least one sign of insulin resistance were randomized to receive metformin (n = 10) or placebo (n = 5). Metformin (Glucophage XR) was given in doses that increased at weekly intervals from 750 mg to 1.5 grams to 2 grams daily. Milk output was determined by weighing their infants before and after feeding plus the weight of any pumped milk. At 2 to 4 weeks of the study, women given placebo had a reduction of 58 mL daily while those who received metformin increased their milk output by 8 mL daily; however this difference was not statistically significant.[10]

Alternate Drugs to Consider

Acarbose, Glipizide, Glyburide, Insulin, Miglitol

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Substance Identification

Substance Name

Metformin

CAS Registry Number

657-24-9

Drug Class

Breast Feeding

Lactation

Milk, Human

Hypoglycemic Agents

Biguanides