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Dothiepin

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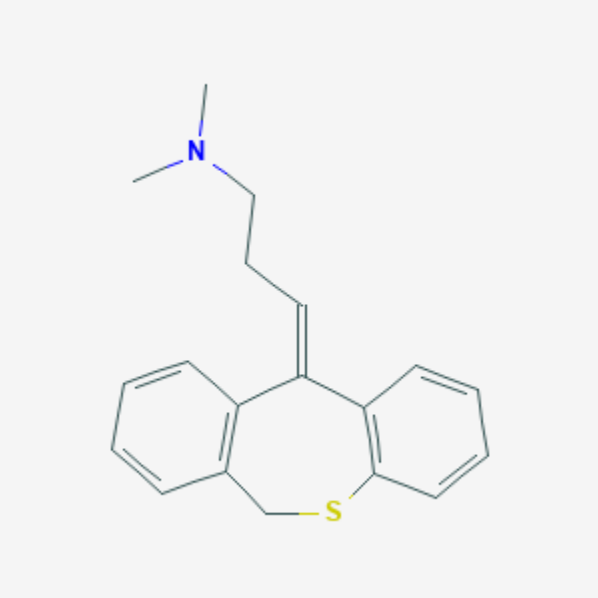
CASRN: 113-53-1



Drug Levels and Effects

Summary of Use during Lactation

Dothiepin is not approved for marketing in the United States by the U.S. Food and Drug Administration, but is available in other countries. Limited information indicates that maternal doses of up to 225 mg daily produce low levels in milk and breastfed infants' serum, and cause no adverse developmental consequences. Dothiepin would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months.

Drug Levels

Dothiepin is metabolized to northiaden (nordothiepin), dothiepin-S-oxide and northiaden-S-oxide. The metabolites are estimated to have activity of about 50% of dothiepin's.[1]

Maternal Levels. A woman was taking dothiepin 25 mg 3 times daily and clorazepate potassium 15 mg at bedtime. A breastmilk sample was obtained 3 hours after the second dose of the day. The dothiepin breastmilk concentration was 33 mcg/L. Another woman who had taken a total of 300 mg of dothiepin over 6 days had a breastmilk dothiepin concentration of 10 mcg/L, but sample collection time was not reported. Metabolites were not measured in either patient.[2]

Eight women who were receiving dothiepin for depression provided breastmilk samples immediately before and after breastfeeding using a breast pump. Maternal dosages ranged from 25 to 225 mg daily (0.38 to 4.5 mg/kg daily) and the duration of therapy ranged from 2 days to more than 5 years. Dothiepin and its metabolites, northiaden, dothiepin-S-oxide and northiaden-S-oxide were measured in milk. The authors calculated weight-adjusted percentages of maternal dosages as follows: 0.58% for dothiepin, 0.23% for nordothiepin, 2.47% for dothiepin-S-oxide and 1.17% for nordothiepin-S-oxide.[3]

Twenty lactating women were taking oral dothiepin once daily for depression in daily dosages of 75 mg to 225 mg. Milk samples were collected 10 to 14 hours after the previous dose of dothiepin which had been constant for at least 12 days. A total of 38 breastmilk samples were obtained because some women donated samples more than once. Dothiepin milk levels ranged from undetectable (<10 mcg/L) to 95 mcg/L and northiaden milk levels ranged from undetectable (<10 mcg/L) to 60 mcg/L with wide variability in both. No statistical difference was found between foremilk and hindmilk levels.[4]

Two mothers with depression who were taking dothiepin had milk samples taken 12 to 15 hours after their daily dose. Milk dothiepin levels were measured by gas chromatography. Foremilk levels were lower than hindmilk levels. The mother taking 225 mg daily had a foremilk level of 988 mcg/L and a hindmilk level of 1250 mcg/L. The second mother provided milk samples on 2 different dosages. While taking 50 mg daily, the foremilk level was 54 mcg/L and the hindmilk level was198 mcg/L. While taking 100 mg daily, the foremilk level was 74 mcg/L and the hindmilk level was121 mcg/L.[5]

Infant Levels. Eight women who were receiving dothiepin for depression were breastfeeding their infants (extent not stated). Infant serum samples were obtained from 5 of the infants. One infant (maternal dosage 0.38 mg/kg daily for 7 days) had no detectable (<2 mcg/L) serum dothiepin or northiaden. In 4 other infants (maternal dosage range 0.95 to 4.5 mg/kg daily for 2 days to 5 years), only dothiepin-S-oxide and northiaden-S-oxide were measured, but not detectable (<10 mcg/L) in their plasma.[3]

Two breastfed (extent not stated) infants whose mothers were taking dothiepin (dosages not stated) had blood and urine samples measured for dothiepin and northiaden. One infant had plasma levels of 34 and 22 mcg/L, respectively, and urine levels of 19 and 15 mcg/L. The other infant had no detectable drug or metabolite in plasma or urine.[4]

Two mothers were breastfeeding (extent not stated) their infants while taking dothiepin. One was taking 50 mg daily and the other was taking 225 mg daily. Urine and blood samples were taken 12 to 15 hours after the mother's dose. Both infants had urine dothiepin concentrations of about 70 ng/L. The infant whose mother was taking 225 mg daily had a serum dothiepin concentration of 4.1 mcg/L, which was 0.16% of the maternal serum concentration. The other infant did not have a blood sample taken.[5]

Effects in Breastfed Infants

Eight women who were receiving dothiepin for depression breastfed (extent not stated) their infants aged 0.13 to 12.5 months of age. Maternal dosages ranged from 25 to 225 mg daily (0.38 to 4.5 mg/kg daily). None of the infants had any noticeable adverse reactions.[3]

A retrospective, case-control study of 15 women who breastfed while taking dothiepin for depression compared the neurocognitive outcomes of their infants to those in a group of 15 depressed mothers who had not taken an

antidepressant during breastfeeding and another 36 women without depression. The mothers in the dothiepin group had taken dosages of 150 to 225 mg daily for 4 to 134 weeks during breastfeeding. Infants had been exposed to dothiepin in breast milk at times from 3 to 152 weeks of age and were assessed at 3 to 5 years of age. There was no evidence of negative effects on the infants' development using a number of rating scales.[6]

Two infants were breastfed for 7 to 18 weeks during maternal use of dothiepin. The drug was started when both infants were 8 weeks of age. One mother started with a dose of 50 mg daily that was increased to 100 mg daily; she took dothiepin for 33 weeks during breastfeeding. The other mother was taking 225 mg daily and nursed her infant for 25 weeks during breastfeeding. Formal testing indicated no adverse effects on infant development up to 30 months of age.[5]

Effects on Lactation and Breastmilk

Galactorrhea has been reported in one woman taking dothiepin.[7]

An observational study looked at outcomes of 2859 women who took an antidepressant during the 2 years prior to pregnancy. Compared to women who did not take an antidepressant during pregnancy, mothers who took an antidepressant during all 3 trimesters of pregnancy were 37% less likely to be breastfeeding upon hospital discharge. Mothers who took an antidepressant only during the third trimester were 75% less likely to be breastfeeding at discharge. Those who took an antidepressant only during the first and second trimesters did not have a reduced likelihood of breastfeeding at discharge.[8] The antidepressants used by the mothers were not specified.

A retrospective cohort study of hospital electronic medical records from 2001 to 2008 compared women who had been dispensed an antidepressant during late gestation (n = 575) to those who had a psychiatric illness but did not receive an antidepressant (n = 1552) and mothers who did not have a psychiatric diagnosis (n = 30,535). Women who received an antidepressant were 37% less likely to be breastfeeding at discharge than women without a psychiatric diagnosis, but no less likely to be breastfeeding than untreated mothers with a psychiatric diagnosis.[9] None of the mothers were taking dothiepin.

Alternate Drugs to Consider

Nortriptyline, Paroxetine, Sertraline

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Substance Identification

Substance Name

Dothiepin

CAS Registry Number

113-53-1

Drug Class

Breast Feeding

Lactation

Antidepressive Agents

Antidepressive Agents, Tricyclic

Adrenergic Uptake Inhibitors