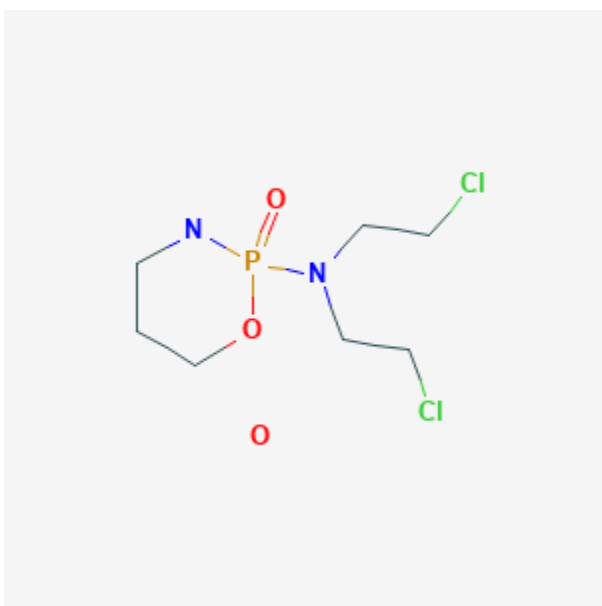




Cyclophosphamide

Revised: March 16, 2020.

CASRN: 6055-19-2



Drug Levels and Effects

Summary of Use during Lactation

Cyclophosphamide appears in milk in potentially toxic amounts; additionally, highly toxic active metabolites could add to the risk to the infant. Neutropenia has been reported in 2 infants whose mothers breastfed them while receiving cyclophosphamide. Chemotherapy may adversely affect the normal microbiome and chemical makeup of breastmilk.[1] Women who receive chemotherapy during pregnancy are more likely to have difficulty nursing their infant. Most sources consider breastfeeding to be contraindicated during maternal cytotoxic antineoplastic drug therapy, especially alkylating agents such as cyclophosphamide.[2] It appears to take more than 21 days for the drug and its metabolites to be eliminated from breastmilk. Some authors' data suggest that it might take 6 weeks for milk levels to drop to a safe level after a dose of cyclophosphamide 750 mg/sq. m.[3]

Drug Levels

Maternal Levels. Unmetabolized cyclophosphamide was qualitatively detected in milk 1, 3, 5 and 6 hours after IV injection of 500 mg of drug in one patient.[4,5] Quantitative determination was not reported.

A mother who had been exclusively breastfeeding for 6 months was diagnosed with multiple sclerosis. In preparation for stem cell transplantation, she received intravenous cyclophosphamide 2.8 grams daily for 4 consecutive days. She was also receiving anti-thymocyte immune globulin, methylprednisolone, mesna, and furosemide. She provided milk samples several times on each of the 4 days for analysis of cyclophosphamide. No metabolites, including active metabolites, were measured. Peak cyclophosphamide milk levels occurred at 4 to 5 hours each day. However, the level of exposure was lower on each successive day, presumably because of autoinduction of the drug's metabolism. Peak level ranged from 40.8 mg/L on day 1 to 13.2 mg/L on day 4; the average level ranged from 15.1 mg/L on day 1 to 3.1 mg/L on day 4; and, the estimated daily infant dosage ranged from 2.3 mg/kg on day 1 to 0.5 mg/kg on day 4. The weight-adjusted percentage of the maternal dosage ranged from 4.8% on day 1 to 0.9% on day 4.[6]

A woman was diagnosed with B-cell non-Hodgkins lymphoma at 4 months postpartum. She received R-CHOP therapy every 21 days for 6 cycles. It consisted of rituximab 375 mg/sq. m, cyclophosphamide 750 mg/sq. m, doxorubicin 50 mg/sq. m, vincristine 1.4 mg/sq. m (capped at 2 mg) plus prednisone 40 mg/sq. m daily. She also received oral 300 mg of allopurinol daily during the whole therapy course. Milk samples were collected twice daily during the first 3 cycles then once daily for the remaining cycles for a total of 290 samples. Cyclophosphamide was detectable in milk shortly after administration, with the peak milk level of over 1 mg/L occurring shortly after the first dose. The toxic metabolites, 4-ketocyclophosphamide, 4-hydroxycyclophosphamide, carboxycyclophosphamide, and N-dechloroethylcyclophosphamide were also detectable in milk. Cyclophosphamide dropped to low levels after a week, but the drug and some of its toxic metabolites were still detectable at 21 days after the dose.[3]

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

Effects in Breastfed Infants

In one 23-day-old infant, neutropenia, thrombocytopenia and a low hemoglobin were possibly caused by cyclophosphamide after 3 days of maternal treatment with cyclophosphamide 6 mg/kg IV daily (total dose 300 mg).[7]

In a 4-month-old, neutropenia was probably caused by cyclophosphamide in a mother 9 days after the last of 6 weekly doses of 800 mg cyclophosphamide intravenously, 2 mg vincristine intravenously and daily doses of 30 mg of prednisolone orally. Neutropenia persisted at least 12 days and was accompanied by a brief episode of diarrhea.[8]

Effects on Lactation and Breastmilk

Telephone follow-up study was conducted on 74 women who received cancer chemotherapy at one center during the second or third trimester of pregnancy to determine if they were successful at breastfeeding postpartum. Only 34% of the women were able to exclusively breastfeed their infants, and 66% of the women reported experiencing breastfeeding difficulties. This was in comparison to a 91% breastfeeding success rate in 22 other mothers diagnosed during pregnancy, but not treated with chemotherapy. Other statistically significant correlations included: 1. mothers with breastfeeding difficulties had an average of 5.5 cycles of chemotherapy compared with 3.8 cycles among mothers who had no difficulties; and 2. mothers with breastfeeding difficulties received their first cycle of chemotherapy on average 3.4 weeks earlier in pregnancy. Of the 56 women who received a cyclophosphamide-containing regimen, 34 had breastfeeding difficulties.[9]

References

1. Pistilli B, Bellettini G, Giovannetti E, et al. Chemotherapy, targeted agents, antiemetics and growth-factors in human milk: How should we counsel cancer patients about breastfeeding? *Cancer Treat Rev.* 2013;39:207–11. PubMed PMID: 23199900.
2. Urbaniak C, McMillan A, Angelini M, et al. Effect of chemotherapy on the microbiota and metabolome of human milk, a case report. *Microbiome.* 2014;2:24. PubMed PMID: 25061513.
3. Codacci-Pisanelli G, Honeywell RJ, Asselin N, et al. Breastfeeding during R-CHOP chemotherapy: Please abstain! *Eur J Cancer.* 2019;119:107–11. PubMed PMID: 31437753.
4. Duncan JH, Colvin OM, Fenselau C. Mass spectrometric study of the distribution of cyclophosphamide in humans. *Toxicol Appl Pharmacol.* 1973;24:317–23. PubMed PMID: 4741053.
5. Wiernik PH, Duncan JH. Cyclophosphamide in human milk. *Lancet.* 1971;297:912. PubMed PMID: 4102054.
6. Fierro ME, Datta P, Rewers-Felkins K, et al. Cyclophosphamide use in multiple sclerosis: Levels detected in human milk. *Breastfeed Med.* 2019;14:128–30. PubMed PMID: 30589584.
7. Durodola JI. Administration of cyclophosphamide during late pregnancy and early lactation: A case report. *J Natl Med Assoc.* 1979;71:165–6. PubMed PMID: 423292.
8. Amato D, Niblett JS. Neutropenia from cyclophosphamide in breast milk. *Med J Aust.* 1977;1:383–4. PubMed PMID: 859486.
9. Stopenski S, Aslam A, Zhang X, et al. After chemotherapy treatment for maternal cancer during pregnancy, is breastfeeding possible? *Breastfeed Med.* 2017;12:91–7. PubMed PMID: 28170295.

Substance Identification

Substance Name

Cyclophosphamide

CAS Registry Number

6055-19-2

Drug Class

Breast Feeding

Lactation

Antineoplastic Agents

Alkylating Agents