Excretion of Hydroxyurea Into Milk

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This article documents that hydroxyurea (HUR) is excreted into human breast milk, and it reviews the literature describing similar evaluations for other antineoplastic agents.
***Cancer* 60:2177–2178, 1987.**

PUBLISHED REPORTS that evaluate the excretion of antineoplastic agents into milk are limited. Investigators have studied doxorubicin, cisplatin, methotrexate, and cyclophosphamide in the milk of lactating mothers. This report describes the detection of hydroxyurea (HUR) in the milk of a patient with chronic myelogenous leukemia (CML).

Materials and Methods

The patient was a 29-year-old woman with recently diagnosed, Philadelphia chromosome-positive CML. At the time of diagnosis, she was breast feeding her infant and expressed a desire to continue to do so. We reviewed the literature and found no reports addressing the excretion of hydroxyurea into milk. She was advised to wean her infant and begin treatment with HUR. The patient agreed to wean her child over three days.

Milk samples were collected the day prior to HUR treatment and for the subsequent week. During this time as an outpatient, she was taking 500 mg of HUR (Hydrea, Squibb) orally three times a day. Milk samples were collected 2 hours after the last dose of HUR each day. When milk was collected on the seventh day, blood was drawn and the plasma removed. All samples were kept at −40°C until assayed.

Reagent grade HUR was provided by Calbiochem. The assay technique used on HUR was a modification of the colorimetric analysis described by Belt *et al.*[1] To extract lipids, 2 ml of milk were mixed with 2 ml of chloroform; the samples were spun at 20°C for 45 minutes at 3600 rpm; 1 ml of the aqueous phase was then mixed with 2 ml of 1 M perchloric acid and put on ice for 30 minutes; these samples were spun at 4°C for 30 minutes at 3600 rpm. HUR standards were prepared using pretreatment milk samples.

To each ml of the patient samples and HUR standards the following reagents were added: 0.5 ml buffer (9.7 ml of 0.5 M Na_2HPO_4 + 1.8 ml of 1.5 M NaH_2PO_4 + 8.6 ml H_2O); 0.05 ml 10.3 M NaOH; 0.5 ml 1% sulfanilic acid; 0.05 ml 0.1 N iodine; 0.05 ml 0.1 M $Na_2S_2O_3$; and 0.5 ml naphthyl solution (100 mg N-1 napthylethylenediamine dihydrochloride + 17.5 ml 12 N HCl + 82.5 ml H_2O). The resulting solution was kept at 20°C for 20 minutes. It was read at 540 mu using a Gilford spectrophotometer, which was blanked with a pretreatment milk sample processed as just described. The plasma specimen that was collected on day 7 was not available for analysis because of an error in handling. A graph of the standard curve was used to determine HUR concentrations in breast milk.

Results

The analysis of milk for HUR was technically difficult. Only three of the patient's samples cleared adequately after the extraction process to ensure reliable spectrophotometric readings (Table 1). The HUR milk concentrations for those specimens that completely cleared after the extraction process were day 1—6.1 mg/l; day 3—3.8 mg/l; and day 4—8.4 mg/l. The mean HUR concentration was 6.1 ± 2.3 mg/l.

Discussion

Our data document that HUR administered at a therapeutic dosage is excreted into milk. Given the mean HUR concentration in the milk of our patient, the infant would have received in the range of 3 to 4 mg daily

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The authors thank Dr. Mahmoud M. Abdel-Monem, Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota for his advice and laboratory support; Mr. Frank Jones for technical assistance; and Ms. Sue Krumm and Ms. Julie Sherman for their assistance in manuscript preparation.

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Accepted for publication May 6, 1987.

TABLE 1. Hydroxyurea Concentrations in Milk

Milk sample by day	Hydroxyurea (mg/l)
1	6.1
3	3.8
4	8.4
Mean	6.1 ± 2.3

if beast feeding was continued. This amount is based on a total daily milk yield of 600 ml/day, which has been established for American women.[2]

Data on the excretion of antineoplastic agents into milk is scarce. The excretion of methotrexate, cyclophosphamide, doxurubicin, and cisplatin has been studied by way of lactation. Johns *et al.* described a lactating patient who received 22.5 mg of methotrexate daily for choriocarcinoma. The peak methotrexate level in the milk was 6.0×10^{-9} M.[3] Cyclophosphamide was qualitatively identified in milk samples of a lymphosarcoma patient after she received 500 mg of cyclophosphamide by intravenous bolus.[4] Egan *et al.* collected milk specimens from a woman receiving cisplatin and doxorubicin for ovarian cancer. An analysis of the milk did not reveal cisplatin, but it did show doxorubicin and its metabolite, doxorubicinol.[5]

Although the amounts of methotrexate, cyclophosphamide, doxorubicin, and hydroxyurea recovered in milk samples are small, there is agreement that mothers receiving antineoplastic therapy are best advised to suspend breast-feeding during treatment. The concern that nursing infants will develop toxic reactions caused by ingesting antineoplastic agents through breast milk is illustrated by two cases. Both cases involve mothers who received high doses of cyclophosphamide (800 mg and 900 mg)—their nursing infants experienced bone marrow suppression.[6,7]

In summary, we believe that HUR is excreted into milk. While the daily amount of HUR that the infant in this case might have ingested appears to be low, the effects of such exposure remain undetermined. Consequently, we recommend that lactating mothers treated with HUR do not nurse their infants.

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