Hydroxyurea Exposure in Lactation: a Pharmacokinetics Study (HELPS)

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Lactation is contraindicated for women with sickle cell anemia receiving hydroxyurea therapy, despite sparse pharmacokinetics data. In 16 women who were lactating volunteers, we documented hydroxyurea transferred into breastmilk with a relative infant dosage of 3.4%, which is below the recommended 5%-10% safety threshold. Breastfeeding should be permitted for women taking daily oral hydroxyurea. *(J Pediatr 2020;222:236-9).*

Breastfeeding is considered to be a public health imperative due to the many beneficial health outcomes for both mothers and infants. The American Academy of Pediatrics recommends exclusive breastfeeding for about 6 months, followed by breastfeeding continuation for at least 1 year.[1] Among the reasons that limit breastfeeding initiation and continuation rates, a relatively neglected one is the use of maternal medications listed as lactation contraindications, due to potential or proven risks to the infant.[2] Pediatricians have a responsibility to assist mothers with questions about the safety of medications prescribed for their own health while supporting their desire to breastfeed. Published resources such as LactMed[3] and "Medications and Mother's Milk"[4] can assist pediatricians in assessing the possible effects of maternal medications on the nursing infant, but many drugs have not been adequately tested in the setting of lactation.

Hydroxyurea is the primary Food and Drug Administration–and European Medicines Agency–approved therapy for sickle cell anemia (SCA), with evidence-based guidelines recommending treatment for both adults and children as early as 9 months of age.[5,6] As a ribonucleotide reductase inhibitor with potential teratogenic and mutagenic effects,[7] package inserts for hydroxyurea list pregnancy and lactation as formal treatment contraindications.[8] However, because women with SCA have a high risk of morbidity and mortality during pregnancy and postpartum,[9-12] withholding effective disease-modifying treatment could harm both mothers and their babies.

One 1987 case report documented transfer of hydroxyurea into human breastmilk, describing a mother who was lactating with chronic myelogenous leukemia.[13] She received hydroxyurea 500 mg orally 3 times daily, and measurements 2 hours after the last dose detected hydroxyurea in the breastmilk. Total infant exposure through breastfeeding was ~3-4 mg/day, representing <1% of the mother's daily dose, but the authors recommended that lactating mothers receiving hydroxyurea should not breastfeed their infants.[13]

PK	Pharmacokinetics
RID	Relative infant dosage
SCA	Sickle cell anemia

We recently confirmed hydroxyurea transfer into breastmilk of a lactating mother with SCA, ranging from 4 to 20 μg/mL several hours after her daily dose.[14]

Recognizing that many young women with SCA now receive hydroxyurea treatment during child-bearing years, additional data are needed to understand potential risks of hydroxyurea exposure during lactation. HELPS (Hydoxyurea Exposure in Lactation: a Pharmacokinetics Study; NCT02990598) was designed to address knowledge gaps in lactating healthy volunteers or patients with SCA; the objectives were to obtain blood, urine, and breastmilk samples for pharmacokinetics (PK) analysis using scheduled collections; calculate distribution ratios for hydroxyurea across biological compartments, especially plasma to milk; and create hydroxyurea PK profiles to estimate potential infant drug exposure.

Methods

Adult female volunteers were recruited for single-dose PK analysis, receiving 1000 mg (~15-20 mg/kg) as a one-time oral dose, with no food for 2 hours before or 1 hour after drug administration. Baseline blood, urine, and breastmilk samples were obtained before dosing and then using a frequent collection schedule: blood collection at 15, 30, 60, 120, 180, 240, 360, 480, 540, 720, and 1440 minutes after dosing; breastmilk on the same schedule minus the 15-minute sample, and urine minus the 15-minute and 30-minute time points. Subsequently a 3-hour schedule to mimic physiological feeding was used for blood, urine, and breastmilk collection. At each time point including the baseline, blood was collected for plasma analysis, all available urine was collected, and both breasts were emptied entirely as recommended,[15] using a Symphony

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hospital-grade double electric breast pump (Medela, McHenry, Illinois) and hands-on pumping technique. This breastmilk collection schedule exceeds 6 time points suggested for accurate milk PK analysis.[15]

Hydroxyurea concentrations were measured by validated high-performance liquid chromatography assay, with methylurea internal standard, sensitivity to 0.5 μg/mL, and intraday and interday variability <10%.[14] Data were analyzed to determine milk:plasma distribution ratios, and noncompartmental PK analysis was conducted (WinNonlin Version 4.0.1; Pharsight Corporation, Palo Alto, California) using a weighted least-squares algorithm as described.[16,17] Parameter estimates included maximal concentration, time to maximal concentration, total body clearance, volume of distribution, elimination half-life, mean residence time, and area under the curve.

The daily hydroxyurea intake in breastfed infants was estimated as follows: infant's daily dose = $\sum (C_{avg\_milk} \times Vol_{milk})$, where C_{avg_milk} is the estimated average hydroxyurea concentrations in breastmilk during each scheduled breastfeeding time (every 2 or 3 hours) and Vol_{milk} is the ingested milk volume per feeding, based on an average 150 mL/kg/d.[17] Relative infant dosage (RID) was calculated per the World Health Organization Working Group on Drugs and Human Lactation: RID = infant's daily dosage (mg/kg)/mother's daily dosage (mg/kg).[4,18,19]

Results

Study Cohort

In total, 16 mothers who were lactating were enrolled: 14 healthy volunteers and 2 with SCA not taking daily hydroxyurea. There were 11 white and 5 black women with median age of 32 years (range 27-40 years), median weight of 76.3 kg (range 48.8-115.9 kg), and median body mass index of 26.0 kg/m^2 (range 20.2-39.3 kg/m^2). Study participants were currently breastfeeding for a mean of 9 months, range 2-22 months.

Hydroxyurea PK Analysis

After oral administration, hydroxyurea was detected in the plasma of the first 11 women who were lactating within 15-30 minutes, and peak concentrations of 10-40 μg/mL were measured 60-120 minutes after dosing (**Figure**, A). Similarly, hydroxyurea was detected in the breastmilk within 30 minutes, with measured concentrations 80%-90% of corresponding plasma concentrations, consistent with rapid equilibration between plasma and milk compartments. A small amount of hydroxyurea was detected in breastmilk 12 hours after the dose, but none at 24 hours. The **Table** provides a summary of hydroxyurea PK parameters for the entire study cohort.

The amount of hydroxyurea transferred into the breastmilk was calculated, based on the concentration at each time point multiplied by the volume of milk at each collection. An average total of 2.2 $\pm$ 1.0 mg hydroxyurea was transferred into the breastmilk, including 1.2 mg in the first 3 hours, followed by 0.7 mg in the next 3 hours.

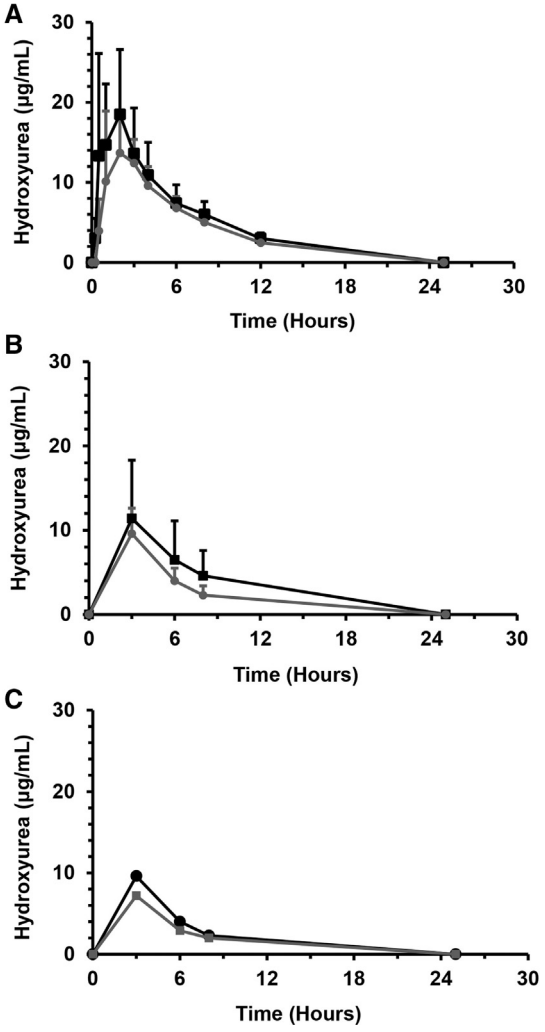

Figure. Hydroxyurea concentration time profiles in plasma (*black lines*) and breastmilk (*gray lines*) in human volunteers. **A,** Average PK curves for the first 11 healthy volunteer study participants. Hydroxyurea was detected in breastmilk within 30 minutes, with an average peak concentration of 10-15 μg/mL at 1-3 hours, and remained at 80%-90% of corresponding plasma concentrations, consistent with rapid equilibration between plasma and milk compartments. A small amount of hydroxyurea (<3 μg/mL) was detected in the breastmilk 12 hours after the dose, but none at 24 hours. **B,** PK curves on 3 additional healthy volunteers conducted using a more physiologically relevant 3-hour collection schedule, with lower peak concentrations reflecting plasma drug excretion without accumulation in the breastmilk. **C,** PK curves in breastmilk for 2 mothers with SCA and 3 normal volunteers, with no significant differences observed.

Delayed-Collection Schedule

Because natural breastfeeding does not occur at such frequent intervals, a schedule of 3-hour collections was then conducted on the next 5 women to mimic physiological feeding. For 3 normal volunteers, peak concentrations at 3 hours were lower, reflecting rapid drug excretion from

Table. Hydroxyurea PK parameters in women who were lactating

Study participants	BF, mo	Volume, mL	Drug, mg	C_{max}, μg/mL		T_{max}, h		AUC_{last}, μg*h/mL		CL/F, L/h		Half-life, h		MRT, h		V/F, L	
				Plasma	Milk	Plasma	Milk	Plasma	Milk	Plasma	Milk	Plasma	Milk	Plasma	Milk	Plasma	Milk
1	8.3	425	2.96	34.8	17.3	2.0	2.0	132.6	97.5	7.8	11.9	3.0	3.4	3.3	5.0	36.7	63.2
2	4.0	467	1.64	10.4	9.8	2.0	2.1	42.3	53.2	12.6	13.4	4.1	3.1	3.5	5.0	68.4	54.3
3	9.3	326	3.23	38.1	23.0	0.5	0.9	91.8	102.8	9.7	9.1	4.3	5.6	2.7	4.1	64.6	78.2
4	19.9	50	0.23	15.0	10.3	2.0	3.6	62.3	61.2	9.8	13.6	4.7	3.5	3.5	5.0	64.5	66.8
5	4.7	480	2.73	18.4	10.4	2.0	3.0	83.2	68.0	7.3	10.4	3.9	4.1	3.7	5.3	40.1	59.9
6	8.7	314	2.44	21.7	18.2	2.0	1.1	95.5	93.9	9.6	11.3	3.4	4.4	3.0	4.3	49.7	76.8
7	12.6	134	1.17	17.0	14.6	1.0	2.1	71.0	93.2	11.0	10.3	4.5	5.9	3.0	5.0	76.5	92.8
8	9.8	478	2.11	12.5	9.9	1.0	1.9	48.6	48.5	15.2	16.1	3.8	2.8	3.6	4.1	81.6	64.2
9	5.3	638	1.46	23.8	10.7	2.1	2.0	91.9	27.0	8.2	30.0	2.8	1.2	3.7	2.9	32.1	50.3
10	4.1	520	1.93	22.6	16.9	1.0	1.0	88.6	64.1	8.4	11.6	2.9	2.7	3.4	3.5	33.5	41.9
11	3.0	573	3.89	28.1	21.4	0.5	1.0	103.7	86.1	7.8	9.1	3.7	4.0	3.3	3.5	40.7	51.3
12	11.4	235	1.01	18.5	11.3	1.0	3.0	57.8	46.6	12.2	NC	2.9	NC	2.9	4.3	48.5	NC
13	22.1	280	1.41	19.3	11.3	3.2	2.8	104.3	53.9	NC	NC	NC	NC	4.8	4.5	NC	NC
14	2.5	352	0.91	6.8	6.2	3.0	3.0	37.0	27.4	NC	NC	NC	NC	4.8	4.5	NC	NC
15	3.5	154	0.057	6.6	7.2	3.0	3.0	26.5	30.0	NC	NC	NC	NC	3.9	4.3	NC	NC
16	6.5	14	0.022	18.3	8.2	1.0	3.0	59.2	46.2	10.5	NC	2.6	NC	2.9	5.0	34.2	NC
Mean	8.6	340	1.70	19.5	12.9	1.7	2.2	74.8	62.5	10.0	13.4	2.9	3.7	3.5	4.4	51.6	63.6
SD	5.6	186	1.15	8.9	5.0	0.9	0.9	28.9	25.6	2.3	5.9	1.6	1.3	0.6	0.7	17.4	14.7

AUC_{last}, area under the curve; *BF*, duration of breastfeeding; *CL/F*, apparent hydroxyurea clearance from plasma or breastmilk; *C_{max}*, maximum concentration in plasma or breastmilk; *F*, bioavailability (systemic availability of the administered dose); *MRT*, mean residence time; *NC*, not calculated; *T_{max}*, time to maximum concentration; *V/F*, apparent volume of distribution.
Study participants 1-11 were healthy volunteers with frequent sample collections; 12-14 had 3-hour sample collections; and 15-16 were women with SCA. Volume refers to the total amount of breastmilk (mL) collected for analysis; drug refers to the actual measured amount of hydroxyurea (mg) in the milk; results are shown for each study participant and then summarized as mean (SD).

plasma without accumulation in breastmilk (**Figure**, B). No significant differences were noted in hydroxyurea PK parameters between 3 healthy volunteers and 2 mothers with SCA (**Figure**, C). With this collection schedule, the total amount of hydroxyurea transferred into breastmilk was reduced by 50% to 1.1 mg, by avoiding greater early concentrations in both plasma and milk compartments.

Urinary Excretion

Analysis of urine documented that large amounts of hydroxyurea are excreted unchanged by renal clearance. An average of 542 ± 178 mg (range 295-876 mg) of the 1000-mg dose was detected in 24-hour urine collections, and >90% of the renal excretion occurred within 9 hours after dosing.

PK Analysis

To estimate hydroxyurea in the milk compartment, PK analysis was performed using 150 mL/kg volume of breastmilk consumed per 24 hours, which is standard for early months of life.[20] Calculated daily hydroxyurea exposure through breastfeeding was 0.46 ± 0.16 mg per infant kg, with 50% occurring in the first 3 hours after maternal dosing. The hydroxyurea RID was calculated at 3.4%, below the suggested 10% World Health Organization safety threshold and the more conservative 5% threshold generally considered to be safe.[21,22]

Discussion

The prospective study provides novel and important data regarding transfer of hydroxyurea into human breastmilk and estimated infant drug exposure. In normal volunteers and women with SCA, rapid bidirectional equilibration of drug occurs between plasma and milk compartments, with hydroxyurea initially moving into breastmilk but then moving back into the bloodstream. With physiological feedings every 2-3 hours, the hydroxyurea RID is only 3.4%, which is below the recommended safety thresholds.[4] However, if mothers with SCA take their hydroxyurea dose and then discard the next feeding ("pump-and-dump" technique), the hydroxyurea transferred through breastmilk is further reduced by 50%. In this scenario, infant exposures would be < 1 mg/kg/day, well below ~20-30 mg/kg/day doses that are currently used to treat young infants with SCA.[23,24] These data provide evidence that lactation should not be contraindicated for women with SCA receiving daily hydroxyurea. Hematologists can prescribe daily hydroxyurea as disease-modifying treatment for women with SCA during lactation, because only small amounts of hydroxyurea will transfer to their babies through breastfeeding. Additional data regarding maternal and infant outcomes are being collected in the Hydroxyurea Exposure Limiting Pregnancy and Follow-Up Lactation observational study (HELPFUL, NCT04093986). ■

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