

Glecaprevir/Pibrentasvir Concentrations in the Breastmilk of Lactating Women

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In this prospective pharmacokinetic study of women undergoing chronic hepatitis C virus treatment with glecaprevir/pibrentasvir, the mean glecaprevir and pibrentasvir concentrations in breastmilk were 0.63% and 4.23% of maternal plasma concentrations, with a mean relative infant dose of 0.02% and 0.06%, respectively.

Keywords. Hepatitis C Virus; breastmilk; postpartum; glecaprevir; pibrentasvir.

Universal hepatitis C virus (HCV) screening is recommended for all pregnant individuals during pregnancy with linkage to care for infected mothers and exposed infants [1]. While the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD) have recently changed recommendations to incorporate direct-acting antiviral (DAA) therapy during pregnancy as an option, they provide no guidance for breastfeeding [2]. The American College of Obstetricians and Gynecologists does not recommend initiating treatment during lactation due to lack of safety data [1]. Existing pharmacokinetic data show very low breastmilk concentrations of sofosbuvir/velpatasvir in postpartum women with HCV [3]. However, there are no such data for glecaprevir/pibrentasvir (GLE/PIB), another pan-genotypic DAA

frequently preferred due to its shorter treatment duration (8 vs 12 weeks). Drug transfer into breastmilk is a key factor when assessing drug safety in lactating women. Drug characteristics that promote low breastmilk concentrations include large volume of distribution, high protein binding, low lipid solubility, short elimination half-life, and large molecular weight [4].

The aim of this study was to quantify breastmilk transfer of GLE and PIB in postpartum women being treated for chronic HCV. We hypothesized that the relative infant dose (%RID) (defined as the weight-adjusted percentage of the maternal dosage) of GLE and PIB ingested by a fully breastfed infant would be minimal.

MATERIALS AND METHODS

Participants were eligible for the study if they were 18 years of age or older, postpartum, lactating, and reporting adherence to GLE 100 mg/PIB 40 mg orally, 3 tablets once daily for chronic HCV infection. All approached patients had previously agreed to initiate GLE/PIB using a shared decision-making approach with their medical team as part of routine clinical care. This study was approved by the Washington University Human Research Protection Office (IRB#202510025). All participants provided written informed consent prior to any study procedures. The following clinical data were collected: age, race, ethnicity, time in pregnancy/postpartum period when GLE/PIB was initiated, and duration of GLE/PIB therapy prior to sample collection. Paired maternal blood and breastmilk samples were obtained postpartum after at least 2 daily doses of GLE/PIB. Blood samples were collected within 15 minutes of breastmilk collection.

Concentrations of GLE and PIB in both whole breastmilk and plasma were assessed using liquid chromatography–tandem mass spectrometry (LC-MS/MS) assay as described below.

Reagents

GLE and PIB standards were purchased from Sigma-Aldrich (St Louis, MO, USA). LC-MS grade water, methanol, acetonitrile, and 0.1% formic acid in water were purchased from Fisher Scientific (Fair Lawn, NJ, USA); reserpine and formic acid were purchased from Sigma-Aldrich.

Sample Preparation

For serum samples, 200 μ L of methanol containing 12.6 ng of reserpine as the internal standard was added to the serum sample for forming serum protein precipitation. Samples were vigorously vortexed and centrifuged at 4°C for 10 minutes at 8000 rpm. The supernatant was collected for LC-MS/MS analysis. Four-point calibration samples were also prepared with

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sample amount of reserpine (12.6 ng) in 250 μ L of methanol/water (4:1) solution.

Breastmilk samples were prepared with a modified Bligh–Dyer extraction method: 500 μ L of breastmilk was pipetted in a microcentrifuge tube, and 500 μ L of methanol containing 2.1 ng of reserpine and 500 μ L of chloroform were added to the tube. The sample tube was vigorously vortexed several times and was rotated at 45 rpm for 1 hour at room temperature. Then, the sample was centrifuged at 4°C for 10 minutes at 10 000 rpm. The bottom layer (CHCl_3 layer, 400 μ L) was collected for LC-MS/MS run. Five-point calibration samples, containing 2.1 ng of reserpine, were also prepared for absolute quantification.

Analyte Measurement

Chromatographic separation of GLE, PIB, and reserpine, was achieved using a reverse-phase Zorbax Eclipse Plus C18, 50 $\times$ 2.1 mm column with a 3.5- μ m particle size (Agilent Technologies, Santa Clara, CA, USA) connected to a Shimadzu Nexera 20ADX2 LC system (Shimadzu, Kyoto, Japan) interfaced with API 4000 triple quadrupole mass analyzer (SCIEX, Redwood City, CA, USA) operated in positive ionization and selective reaction monitoring modes. The mobile phase for chromatography consisted of 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in 80:20 acetonitrile:methanol (mobile phase B). The chromatographic method included a gradient elution from 50% to 100% mobile phase B over 3.0 minutes, followed by moving down to 50% mobile phase B for 0.1 minute, then a hold at 50% mobile phase B for 2 minutes until the next sample injection. GLE and PIB were eluted at 1.98 and 3.05 minutes, respectively. Transitions monitored for analytes of interest were as follows: GLE, 839.45 $\rightarrow$ 684.3 m/z; PIB, 557.5 $\rightarrow$ 871.6 m/z; reserpine, 609.3 $\rightarrow$ 195.1 m/z.

Data Analysis

Data were acquired using Analyst 1.6.3 software (SCIEX). Calculations were performed using Microsoft Office Excel software. Infant daily dose was calculated using an average milk intake of 150 mL/kg/day for an exclusively breastfed infant. The relative infant dose (RID) was calculated as $\text{RID} = \text{absolute infant dose (mg/kg/day)} / \text{maternal dose (mg/kg/day)}$, assuming an adult weight of 70 kg. Data were summarized using descriptive statistics.

RESULTS

Five participants were approached; all agreed to participate and enrolled in this breastmilk transfer study. Four participants were White, 1 was Black, and all were of non-Hispanic ethnicity. Three of the 5 participants started treatment in the late third trimester of pregnancy while 2 started postpartum. Paired maternal plasma and breastmilk sampling occurred at a median

time of 4 days after treatment initiation (range, 2–13 days), 4.5 hours after last reported maternal GLE/PIB intake (range, 2.1–7.4 hours), and 2 days postpartum (range, 1–3 days). On review of co-medications for any known drug–drug interactions with GLE/PIB, 1 participant was also receiving famotidine, which may result in decreased concentrations of GLE.

GLE and PIB levels were quantifiable and at therapeutic treatment concentrations in the plasma of 4 of 5 participants. Breastmilk and plasma concentration data from the 1 individual without quantifiable levels in plasma was excluded due to suspected patient nonadherence to GLE/PIB. Table 1 describes maternal plasma and breastmilk concentrations along with milk/plasma concentration ratios and the estimated infant daily dose from breastmilk. GLE and PIB concentrations in breastmilk were 0.63% and 4.23% of maternal plasma concentrations, respectively. The RID from breastmilk was <0.1% for both drugs.

DISCUSSION

This report provides the first data on GLE/PIB concentrations in breastmilk. Our findings indicate that GLE and PIB both cross from the maternal blood circulation into breastmilk at quantifiable levels; however, infant exposure to GLE/PIB via breastmilk appears minimal based on estimated RID. These findings are reassuring for infant safety and support consideration of GLE/PIB during breastfeeding.

Drug excretion into breastmilk depends on the composition of milk, the physiochemical properties of the drug, and the mechanism of transport [5]. The properties of GLE and PIB suggest that amounts expected in breastmilk would be minimal. Both are lipophilic molecules with a molecular weight of 838 g/mol for GLE and a molecular weight of 1113.2 g/mol for PIB. Both are highly bound to maternal plasma proteins: GLE at 97.5% and PIB at >99.9% [6]. Our data provide real-world evidence that the relative infant dose in an exclusively breastfed infant would be expected to meet criteria as minimal [7].

These data are critical given low rates of maternal linkage to postpartum HCV treatment; a recent study showed that only 6% of Medicaid recipients with HCV and opioid use disorder (OUD) receive HCV care within 6 months of delivery [8]. In a nationwide claims database study, among people with HCV and OUD, those with recent pregnancy were significantly less likely to receive DAAs than nonpregnant individuals [9]. In clinical practice, clinicians may adopt a precautionary approach by discontinuing the prescription of inadequately tested medications during breastfeeding or by advising mothers to cease breastfeeding. This approach carries significant consequences for both the mother who may be lost to HCV care, and her child if breastfeeding is discouraged. Deferring treatment until cessation of breastfeeding may contribute to poor rates of HCV treatment, driven by loss to follow-up in the postpartum period. The data in this report on the low rates of

Table 1. Glecaprevir, and Pibrentasvir Concentrations in Plasma and Breastmilk

Drug	Plasma Concentration, ng/mL	Breastmilk Concentration, ng/mL	Milk/Plasma Concentration Ratio	Estimated Infant Daily Dose From Breastmilk, mg/kg/d	% Relative Infant Dose
Glecaprevir	817 (722, 1724)	5.17 (2, 7.28)	0.0063 (0.0028, 0.0042)	0.0009 (0.0003, 0.0011)	0.0210% (0.0070%, 0.0255%)
Pibrentasvir	166 (136.5, 234)	7.035 (2.11, 41.7)	0.0423 (0.0155, 0.1782)	0.0011 (0.0003, 0.0014)	0.0641% (0.0185%, 0.3649%)

Concentrations, ratios, estimated dose, and relative infant dose are shown as mean (minimum, maximum). Total adult daily dose of glecaprevir is 300 mg normalized to 70 kg adult. Total adult daily dose of pibrentasvir is 120 mg normalized to 70 kg adult.

breastmilk transfer of GLE/PIB support infant safety and reinforce its potential as a key HCV treatment that should be offered to patients in a shared decision-making model in the postpartum period.

This report is subject to several limitations. First, the sample size of participants was small. Second, one of the sample sets was collected after only 2 days of treatment, which may be prior to steady state. Third, samples were collected during the first week postpartum when the composition of breastmilk may be evolving and may differ from breastmilk from lactating women with an established milk supply.

These findings provide the first preliminary data on quantification of GLE/PIB in breastmilk. They demonstrate that it is excreted into breastmilk at levels that would be classified as minimal based on relative infant dose safety standards. These data have the potential to inform conversations between providers and lactating women who may be concerned about infant exposure to GLE/PIB. Following shared decision-making, clinicians should consider offering HCV treatment in the immediate postpartum period regardless of lactation. In this context, GLE/PIB can be initiated upon discharge from the hospital after delivery, overcoming barriers in loss to follow-up.

Notes

Author contributions. M. R. C., L. R. M., L. M. M., J. K., and M. J. D. conceived the study. T. H.-B., L. R. M., M. R. C., and L. M. M. coordinated patient consent and sample collection. H. F., J. R., and J. P. H. conducted specimen processing and mass spectrometric analyses, prepared the data, and interpreted spectra. L. R. M. and L. M. M. wrote the first draft of the paper. All authors have approved of and have agreed to submit the manuscript.

Data availability. All data are available from the authors upon reasonable request and establishment of a data use agreement.

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