CHEST

The Direct Factor Xa Inhibitor Rivaroxaban Passes Into Human Breast Milk

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Thromboembolic disorders frequently require antithrombotic treatment during pregnancy and lactation. Vitamin K antagonists and heparins are the treatment options of choice in breastfeeding women. Factors including the route of administration, discomfort during treatment, and fetal and neonatal safety affect women's choices about anticoagulant therapy. Direct-acting oral anticoagulants (DOACs) have emerged as alternatives to these agents and may offer advantages compared with vitamin K antagonists. As breastfeeding women were excluded from clinical trials evaluating DOACs, no safety and efficacy data are available for these special patients and, crucially, estimates for infant exposure are lacking. Therefore, the manufacturer recommends against using DOACs during the lactation period. We present the case of a patient who stopped breastfeeding owing to a diagnosis of postpartum cardiomyopathy. Anticoagulation with enoxaparin that commenced after the diagnosis of postpartum pulmonary embolism was switched to rivaroxaban. At that time, breast milk samples were collected and rivaroxaban concentrations were determined by liquid chromatography tandem-mass spectrometry. Rivaroxaban appears in human breast milk in comparatively small amounts; its safety has not been determined.

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KEY WORDS: breastfeeding; lactation; liquid chromatography tandem-mass spectrometry; pulmonary embolism; rivaroxaban

The use of anticoagulants during pregnancy and the lactation period is challenging as factors that potentially affect the health of both mother and child have to be considered.[1] Direct-acting oral anticoagulants (DOACs) have been established for the medical management of thromboembolic disorders. The safety of DOACs in special patients such as breastfeeding women largely have not been addressed.[2] Data from animal studies suggest that these agents are excreted during lactation, whereas specific human data are lacking.[3] Currently, unfractionated heparin, low-molecular-weight heparins, and vitamin K antagonists are recommended as safe options for breastfeeding women who require anticoagulant therapy.[1]

Case Presentation

Here, we report a 40-year-old white woman (84 kg body weight) with a history of arterial hypertension and hypothyroidism,

ABBREVIATIONS: DOACs = direct-acting oral anticoagulants

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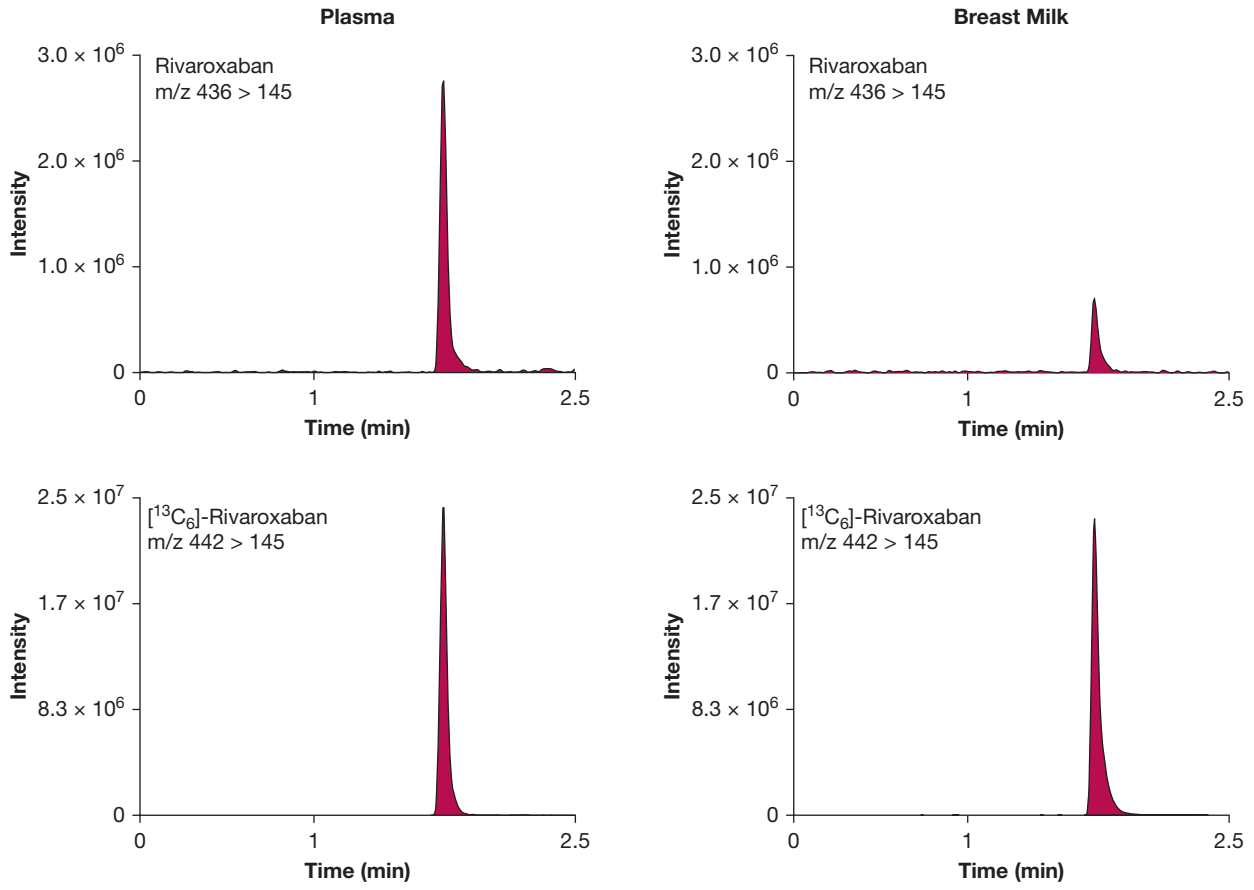

Figure 1 – *Chromatograms of rivaroxaban and $^{13}C_6$-rivaroxaban of an extracted plasma and breast milk sample from the patient obtained before the next rivaroxaban morning dose (trough levels).*

who underwent emergency cesarean surgery owing to placental abruption at 30.5 weeks of gestation. On the fifth day after delivery of a preterm female neonate (1.34 kg body weight), the patient was transferred to our cardiovascular intermediate care facility because of acute dyspnea and chest tightness. Diagnostic imaging scans by CT pulmonary angiography and elevation of troponin T (0.018 µg/L) and N-terminal pro B-type

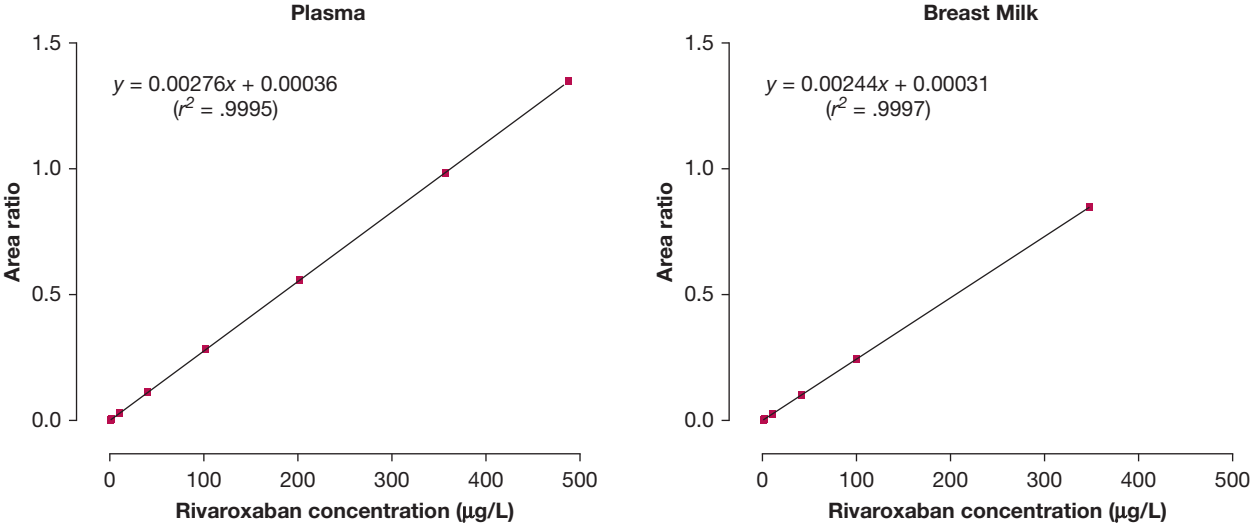

Figure 2 – *Representative rivaroxaban calibration curves derived from plasma calibration standards (linear range, 1-500 µg/L) and breast milk calibration standards (linear range, 1-350 µg/L).*

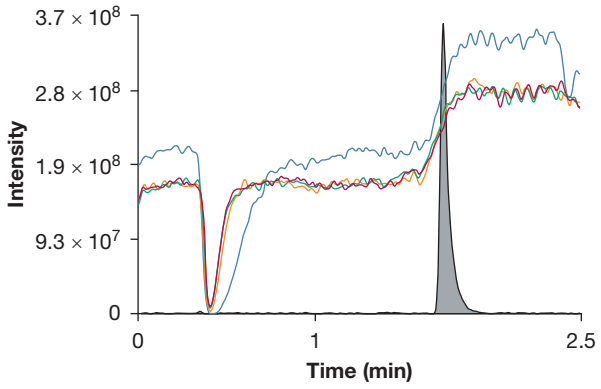

Figure 3 – *Profiles of rivaroxaban signal intensities obtained during direct and continuous infusion of rivaroxaban stock solution into the mass spectrometer (post-column infusion). Simultaneously, extracted blank breast milk and plasma samples (not containing rivaroxaban) were subjected to liquid chromatography tandem-mass spectrometry analysis. Colored lines depict relative changes in rivaroxaban signal intensities caused by eluted blank breast milk and plasma components interfering with the mass spectrometric detection of rivaroxaban (red, orange, and green lines: blank breast milk samples from three otherwise healthy women at the first week postpartum; blue line: representative blank plasma sample). Comparable drifts and shifts of rivaroxaban signal intensities were observed in all experiments. Chromatographic separation of rivaroxaban in extracted patient samples occurs at 1.7 min (representative chromatogram is behind) and thus beyond the maximum drop of signal intensity observed at 0.4 min run time.*

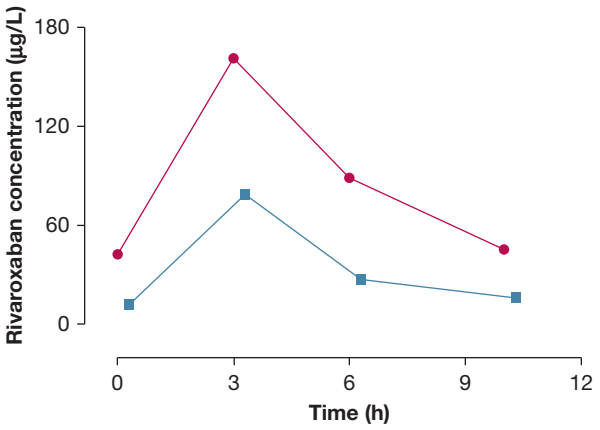

Figure 4 – *Observed plasma (red line) and breast milk (blue line) concentration-time profile of rivaroxaban across the 10-h sample collection interval. Filled circles indicate observed rivaroxaban plasma concentrations. Squares indicate corresponding mean rivaroxaban concentrations determined in breast milk samples by liquid chromatography tandem-mass spectrometry analysis.*

natriuretic peptide (2,543 ng/L) confirmed submassive bilateral pulmonary embolism. Anticoagulant therapy was initiated with enoxaparin at a weight-adjusted dose of 80 mg bid. During the course, the patient showed marked dyspnea and fatigue (New York Heart Association II to III). Transthoracic echocardiography revealed left ventricular dysfunction (ejection fraction, 41%) and mild left ventricular dilatation (58 mm). Cardiovascular MRI scan did not reveal evidence of myocardial inflammation or myocarditis. In the absence of any other cause of heart failure, peripartum cardiomyopathy was diagnosed as the most likely underlying condition. The patient was advised to stop breastfeeding, and treatment of heart failure and hypertension was escalated with metoprolol, hydrochlorothiazide, and ramipril. The patient declined oral antithrombotic treatment with vitamin K antagonists and regular monitoring of the international normalized ratio. Rivaroxaban 15 mg bid was started after 2 days of enoxaparin treatment. In addition, bromocriptine 2.5 mg bid was added according to in-house standards for patients with peripartum cardiomyopathy.

On day 3 of anticoagulant therapy with rivaroxaban and before bromocriptine administration, whole outputs of both breasts were collected independently by an electric pump before and 3, 6, and 10 h after oral intake of the morning dose. Subsequent to milk collections, venous blood samples were collected into tubes containing sodium citrate. Rivaroxaban concentrations were quantified by means of a previously validated liquid chromatography tandem-mass spectrometry method.[4] To determine rivaroxaban in breast milk matrix, calibration standards were prepared from the pooled breast milk of three otherwise healthy women at the first week postpartum. Representative chromatograms, calibration curves, and assessment of matrix effects in breast milk by means of post-column infusion are shown

TABLE 1] Breast Milk Outputs and Observed Rivaroxaban Concentration Data

	Right Breast		Left Breast		Plasma
Time, h	Milk output, L	$C_{rivaroxaban}$, µg/L	Milk Output, L	$C_{rivaroxaban}$, µg/L	$C_{rivaroxaban}$, µg/L
0	0.036	12.4	0.015	11.7	42.6
3	0.042	86.4	0.008	71.5	161.2
6	0.015	28.4	0.009	26.7	88.7
10	0.016	15.6	0.012	16.7	45.6

C = concentration.

TABLE 2] Calculated Rivaroxaban Exposure Estimates

Parameters	Breast Milk	Plasma
$AUC_{0\text{-}10\ h}$, μg*h/L[a]	383.7	949.2
C_{avg}, μg/L	38.4	94.9
M/P ratio	0.4	
Absolute infant dose, μg/kg/10 h[b]	2.4	
Relative infant dose (%)[c]	1.3	

AUC = area under concentration-time curve; C_{avg} = average concentration ($AUC_{0\text{-}10\ h}$/10 h); [b]M/P ratio = C_{avg} milk/C_{avg} plasma.
[a]The AUC was calculated by means of noncompartmental pharmacokinetic analysis using the linear-trapezoidal rule.
[b]Absolute infant dose was calculated as the product from C_{avg} in milk and an assumed milk intake of 0.0625 L/kg/10 h.
[c]Relative infant dose is the absolute infant dose expressed as a percentage of the weight-adjusted maternal dose (μg/kg/12 h).

in Figures 1 through 3. Informed patient consent was obtained for this study before samples were collected.

Rivaroxaban was detected in breast milk samples, and the observed concentration-time profile resembled that obtained in plasma (Fig 4, Table 1). The ratio of milk to plasma was 0.4. The estimated relative infant dose was 1.3% and thus was below the 10% limit of exposure suggested by Bennett.[5] The daily amount of milk consumed by an infant is about 150 mL/kg/d,[6] and a milk intake of 0.0625 L/kg/10 h was assumed for infant dose calculations across the 10-h sample collection interval. Table 2 lists calculated parameters and exposure estimates.

Discussion

Knowledge of drug disposition in lactating women is important to enable adequate and safe treatment decisions for both mothers and their breastfeeding children. We report a unique case of anticoagulant therapy with rivaroxaban in a postpartum patient and demonstrate that rivaroxaban passes into human breast milk in the early period of lactation. Results must be interpreted with caution as the relative infant dose only estimates the infant's exposure to the drug in milk and does not take the bioavailability of rivaroxaban in the infant into consideration.[7] Moreover, different developmental stages of breastfed infants may influence a drug's pharmacokinetics and thus the exposure to an ingested drug,[8] and potential age-related differences in the pharmacodynamic effects of rivaroxaban in neonates need to be considered.[9] To characterize the infant's exposure precisely, an assay of a drug in blood or urine samples of the breastfed infant would be required. Also, we are unable to determine whether rivaroxaban was taken with a meal,[10] and steady-state pharmacokinetics of rivaroxaban may not have been reached in this patient at the time of sampling. Thus, based on a single case presented here, no conclusions can be drawn regarding the safety of rivaroxaban in nursing mothers and their breastfed infants.

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References

1. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e691S-e736S.
2. Yeh CH, Gross PL, Weitz JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. *Blood*. 2014;124(7):1020-1028.
3. Wang Y, Bajorek B. New oral anticoagulants in practice: pharmacological and practical considerations. *Am J Cardiovasc Drugs*. 2014;14(3):175-189.
4. Blaich C, Müller C, Michels G, Wiesen MH. Multi-analyte analysis of non-vitamin K antagonist oral anticoagulants in human plasma using tandem mass spectrometry. *Clin Chem Lab Med*. 2015;53(12):1981-1990.
5. Bennett PN. Use of the monographs on drugs. In: Bennett PN, ed. *Drugs and Human Lactation*. 2nd ed. Amsterdam, The Netherlands: Elsevier; 1996:67-74.
6. Berlin CM, Briggs GG. Drugs and chemicals in human milk. *Semin Fetal Neonatal Med*. 2005;10(2):149-159.
7. Ilett KF, Watt F, Hackett LP, Kohan R, Teoh S. Assessment of infant dose through milk in a lactating woman taking amisulpride and desvenlafaxine for treatment-resistant depression. *Ther Drug Monit*. 2010;32(6):704-707.
8. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003;349(12):1157-1167.
9. Attard C, Monagle P, Kubitza D, Ignjatovic V. The in-vitro anticoagulant effect of rivaroxaban in neonates. *Blood Coagul Fibrinolysis*. 2014;25(3):237-240.
10. Stampfuss J, Kubitza D, Becka M, Mueck W. The effect of food on the absorption and pharmacokinetics of rivaroxaban. *Int J Clin Pharmacol Ther*. 2013;51(7):549-561.