Transfer of Apixaban into Human Milk

TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™ at Amarillo

Palika Datta, PhD[1]; Avery Bramnik, BS[1]; Kathleen Rewers-felkins, MS[1]; Kaytlin Krutsh, Pharm D[2]; Teresa Baker, MD[2]; Thomas W Hale, PhD[1]

[1]Department of Pediatrics, [3]Department of Obstetrics and Gynecology,

Texas Tech University Health Sciences Center, Amarillo

Introduction

Apixaban (Eliquis) is a direct oral anticoagulant that selectively inhibits factor Xa, thus reducing thrombin production. Compared to nonpregnant individuals, pregnant and postpartum women have a four to fivefold increased risk of thromboembolism. Anticoagulation in pregnancy can be safely administered with low molecular weight heparin and unfractionated heparin. Apixaban is an attractive alternative, as it is equally efficacious, safe, reversible, and has limited drug and food interactions in non-pregnant adults. However, direct oral anticoagulants are contraindicated in pregnant and lactating women due to minimal clinical data on the effect of these drugs on the fetus, their extent of transfer into breast milk, and potential clinical implications for the breastfed infant.

This study analyzes breast milk samples from three lactating women consuming apixaban 5 mg orally twice per day with the purpose of describing the transfer of apixaban into human milk.

Case Characteristics (n=3)

Characteristics	Patient 1	Patient 2	Patient 3
Maternal Age (y)	28	31	33
Weight (kg)	70.3	88.4	88.4
Gestational age at delivery (wks)	38	36	39
Infant birth weight (g)	3,458	4,224	3,260
Diagnosis for thrombotic events	Deep vein thrombosis in common iliac and femoral veins	Right internal jugular thrombus	Bilateral pulmonary emboli
Time of sample collection (days after treatment initiation)	4	3	12

Methodology

Results

Figure 1: Mean milk concentration-time profile of apixaban following the oral administration of 5 mg twice daily dose. (n=3)

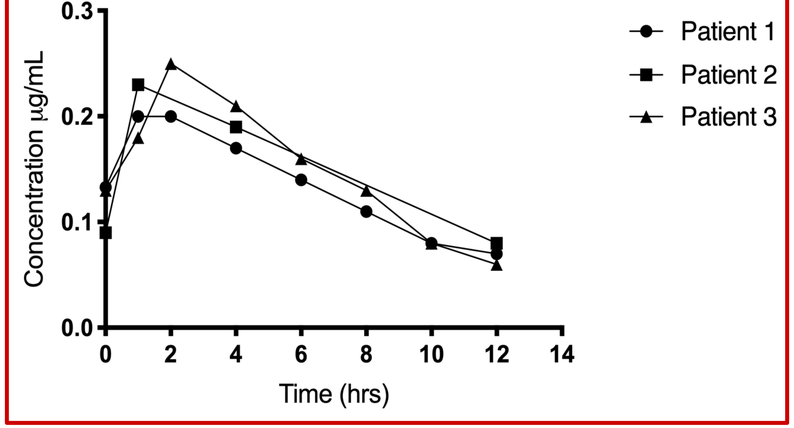

Table 1: The pharmacokinetic parameters of apixaban in human milk.

Parameter	Patient 1	Patient 2	Patient 3
Dose	5 mg twice daily	5 mg twice daily	5 mg twice daily
AUC (µg.hr/mL)	1.637	1.915	1.84
C_{avg} (µg/mL)	0.134	0.16	0.15
C_{max} (µg/mL)	0.2	0.23	0.25
T_{max} (hr)	2	1	2
Infant dose (mg/kg/12 hr)	0.01	0.01	0.01
Relative Infant Dose (%)	**14**	**21**	**20**

Results and Discussion

- The maximum concentration of apixaban in the milk of three mothers was observed at 2 hours after ingestion and averaged 0.23 ± 0.02 µg/mL as shown in Figure 1.
- Based on the assumption of infant's daily milk intake of 75 ml/kg/12hr, the absolute infant dose was calculated to be 0.01 mg/kg/12hr.
- The calculated average relative infant dose (RID) was 18% (range 14–21%). The pharmacokinetic parameters are summarized in Table 1.
- The relative infant dose in all 3 patients was >10%, which suggests high transfer into human milk. In our recently published work, the relative infant dose of rivaroxaban was much lower, ranging from 3-5%.
- Since apixaban and rivaroxaban possess similar chemical and physiological properties, including their lipophilicity, rate of absorption, and degree of protein binding, we would have inaccurately theorized that neither of these drugs would distribute into breast milk significantly.
- Limitations of our study include a small sample size and the absence of corresponding maternal or infant plasma samples. Therefore this study was unable to establish milk to plasma ratio or evaluate if drug secretion into breastmilk reduced the mother's plasma apixaban to subtherapeutic levels.

Conclusion

- Until now there are no studies reported on transfer of apixaban in human milk. This is the first case report on three lactating mothers, suggesting a significant transfer of the drug into milk thereby increasing infant exposure.
- The relative infant dose for apixaban is >10%, above the theoretical level of concern (Bennett,1996), which may signify dangerously high levels being transmitted into milk.
- Further studies describing apixaban's risk to breast milk fed infants and their mothers are needed.
- Data from this study add to the available evidence indicating that other anticoagulants should be preferentially used in breastfeeding mothers until more information is available.

References:

- Bennett, P. N. "Use of the monographs on drugs." Drugs and human lactation 2 (1996): 67-74.