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PHARMACOKINETICS OF OSELTAMIVIR IN BREAST MILK AND MATERNAL PLASMA

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Abstract

Objective—Women in the postpartum period are at high-risk for complications from influenza. Pharmacokinetic data of oseltamivir phosphate in postpartum women, however, are lacking.

Study Design—Seven healthy patients within 48 hours of delivery were recruited. Each woman received 75 mg of oseltamivir phosphate. Plasma and breast milk samples were obtained at times 0, 0.5, 1, 2, 4, 8, 12, and 24 hours after the first dose. The samples were analyzed for oseltamivir and oseltamivir carboxylate levels. Using a noncompartmental model, area-under-the-curve (AUC), maximum concentration (C_{max}), time-to-maximum concentration (T_{max}), and half-life ($T_{1/2}$) were estimated.

Results—Oseltamivir phosphate and oseltamivir carboxylate were found in breast milk, though later and in lower levels than found in plasma. The Cmax and AUC 0–24 was higher for the active metabolite than for the prodrug in both plasma and breast milk.

Conclusion—Oseltamivir carboxylate was present in breast milk but in concentrations significantly lower than considered therapeutic in infants.

Keywords

Oseltamivir; breast milk pharmacokinetics; Oseltamivir excretion

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INTRODUCTION

Increased morbidity and mortality from influenza in pregnancy have been reported for seasonal and pandemic influenza. The 2009 H1N1 pandemic demonstrated that pregnant women are a high risk group with increased rates of hospital admission, intensive care admission and death. (1–10) This high-risk status extends to women in the postpartum period. While it is difficult to say at what time period postpartum a woman's immune system returns to non-pregnant status, the Centers for Disease Control and Prevention (CDC) identified women up to two weeks postpartum as being at increased risk of complications of H1N1 and recommended prompt initiation of antiviral treatment with oseltamivir. (10,11)

Oseltamivir is a neuraminidase inhibitor that is effective against both influenza A and influenza B (12,13) that works by blocking progeny virion release (14–16). It has been shown to reduce the duration of viral replication, the severity and duration of influenza symptoms, the levels of biochemical markers of host inflammatory response, and the incidence of secondary infections. There are no published studies addressing dosing during the postpartum period. Moreover, the only human data regarding transfer of oseltamivir or its active metabolite into breast milk is a published journal correspondence. (17) To provide some guidance on these issues, we studied the pharmacokinetics of first dose oseltamivir in women in the immediate postpartum time period.

MATERIALS & METHODS

This study was approved by the Internal Review Board at the University of Texas Southwestern Medical Center, Dallas, Texas. The study was performed at Parkland Memorial Hospital from March 2010 to May 2010 by the Departments of Obstetrics and Gynecology and Pediatrics at UT Southwestern and in conjunction with the Pediatric Pharmacology Research Unit (PPRU) Network.

Patients age 18 and older without other medical problems following an uncomplicated delivery of a singleton gestation and who had elected to exclusively bottle feed their infants were eligible for the study. Patients were excluded if their delivery was complicated by chorioamnionitis, metritis, or postpartum hemorrhage. Patients were also excluded if they had an allergy or prior adverse reaction to oseltamivir or known kidney or liver disease.

Patients who consented to participate in the study received a single 75 mg capsule of oseltamivir phosphate (Tamiflu). They had blood and breast milk samples collected the time of the first dose of medication and at 0.5, 1, 2, 4, 8, 12, and 24 hours after the single dose of oseltamivir. Blood samples were processed to separate plasma, and plasma and breast milk samples were stored at −80° Celsius for batch analysis.

Plasma and breast milk samples were shipped to BASI Laboratory (United Kingdom) and analyzed for oseltamivir phosphate and oseltamivir carboxylate content using a validated tandem mass spectrometric method (method on file). The method was accurate and sensitive ranging from 1 to 10 ng/mL (RSD < 5%) for oseltamivir phosphate and oseltamivir carboxylate, respectively.

Oseltamivir and oseltamivir carboxylate concentrations (ng/mL) in plasma and breast milk were plotted versus time (hours) for each of the respective subjects. Using a noncompartmental model, area-under-the-curve (AUC), maximum concentration (C_{max}), time-to-maximum concentration (T_{max}), and half-life ($T_{1/2}$) were estimated using Thermo Kinetica 5.0 (Thermo Fischer Scientific, Waltham, MA). The pharmacokinetic estimates were summarized. An Analyses of Variance and Ryan-Einot-Gabriel-Welsh Multiple Range Test were used to determine significance between study variables (SAS 9.2, Cary NC).

RESULTS

Seven women were enrolled who were exclusively bottle feeding. Of the seven patients enrolled, they ranged in age from 19–24 years of age. Six of the seven women enrolled were multiparous, and their BMI ranged from 19–36. Three patients were African American, two were Hispanic, and two were Caucasian. These women were enrolled when the authors were available to perform the multiple sample collections.

We observed both the oseltamivir phosphate prodrug and the oseltamivir carboxylate active metabolite in breast milk (Table 1). As shown in Figures 1 and 2, both oseltamivir phosphate and oseltamivir carboxylate were found in detectible amounts in breast milk later than in plasma, and the breast milk levels of both the prodrug and active metabolite were lower than those in plasma. Individual data are available on request.

Table 1 details the first dose pharmacokinetics indices for oseltamivir phosphate and oseltamivir carboxylate in plasma and in breast milk. The C_{max} (ng/mL) and $AUC_{0–24}$ (ng·hr/mL) for the active metabolite were higher than for the prodrug in both plasma and breast milk. Similarly, the time to reach maximum concentration was higher for the active metabolite than for the prodrug in both plasma and breast milk. The half-life of the active metabolite in breast milk could not be calculated with the collection time points used.

COMMENT

Our data are consistent with the findings in animal models that both the prodrug oseltamivir phosphate and the active metabolite oseltamivir carboxylate are excreted in breast milk. The only prior human data available is from a case report by Wenges-Van Holthe and colleagues who reported a lactating patient treated with oseltamivir for influenza who consented to provide breast milk samples for analysis (17). They found oseltamivir and oseltamivir carboxylase were present in breast milk at low levels corresponding to 0.012 mg/kg to the infant daily, well below pediatric dosing (17).

Our data show following a single dose (75 mg) of oseltamivir, breast milk concentrations of oseltamivir reached a steady state at 12 to 24 hours (Figure 2). We averaged concentrations obtained at 12 and 24 hours to calculate infant exposure; the resulting mean concentration was 2.8 ng/mL. Assuming a 2.75 kg infant ingests 750 mL of breast milk daily, the approximated exposure to oseltamivir is 2.1 micrograms/day or 0.76 microgram/kg/day. When compared with oseltamivir dosing for infants less than 12 months of age (1–7 mg/kg/day) (18), infants exposed to oseltamivir from breast will receive a significantly lower amount of drug (e.g., 1 vs 0.00076 mg/kg/day).

Considering the pharmacokinetics of oseltamivir in plasma in the puerperum, we found values consistent with concentrations achieved in prior reported studies of non-pregnant adults but with some differences in timing. (19) Specifically, the time to achieve maximum oseltamivir concentration was 2.6 ± 2.4 hours in our post partum patients which is longer than the reported 0.9–2.3 hours. For the active metabolite, however, our finding of 4.6 ± 1.5 hours was consistent with prior reports in non-pregnant adults of 3.4–4.6 hours. Similarly, our values for $T_{1/2}$ for both oseltamivir (4.2 ± 2.4) and oseltamivir carboxylate (16.0 ± 8.) were longer than the half-lives reported in non pregnant adults of 1–3 hours (12,15,18) and 6–10 hours (12,14,18) for oseltamivir and oseltamivir carboxylate, respectively. The observed maximum concentrations in plasma for oseltamivir phosphate and oseltamivir carboxylate following first-dose oseltamivir phosphate were lower than those reported by the manufacturer for non-pregnant patients. (19) We observed values of 70.1 ± 72.6 ng/mL for oseltamivir phosphate and 224.3 ± 40.5 ng/mL of oseltamivir carboxylate. Brewster et al

reported similar values in non-pregnant individuals of 75.1 ng/mL for oseltamivir phosphate and 276 ng/mL for oseltamivir carboxylate. (12)

Our study has several limitations. First, the study was designed to assess the pharmacokinetics after the first dose of medication; we do not have steady state data. Second, our patients were in the immediate postpartum period and had not begun breast feeding; oseltamivir levels may differ in women with established breastfeeding. Colostrums, found initially after delivery, has a higher amino acid and protein concentration but less sugar and fat. This is important as individual drug binding to lipids and proteins differs, affecting drug excretion into breast milk. Higher drug levels may be found in colostrums than in established breast milk if the drug is bound to proteins. Conversely, lipid-soluble drugs may be found in lower concentrations in colostrums. However, this study clearly shows that oseltamivir phosphate and oseltamivir carboxylate are excreted into breast milk though in significantly lower concentrations than those in plasma. The active metabolite, oseltamivir carboxylate, remains detectable in breast milk at 24 hours after initial dosing though at significantly lower valves than equates to therapeutic dosing for infants.

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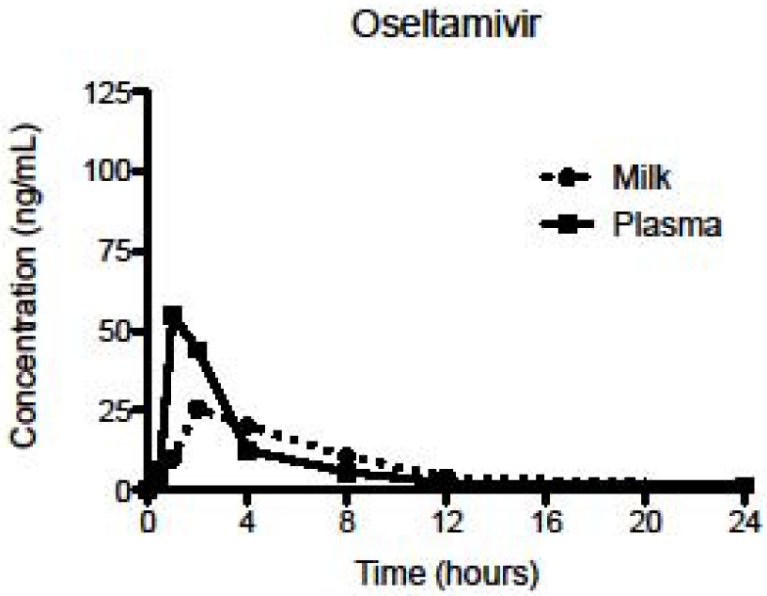

Figure 1.
Mean concentrations of oseltamivir phosphate in plasma and breast milk after first dose.

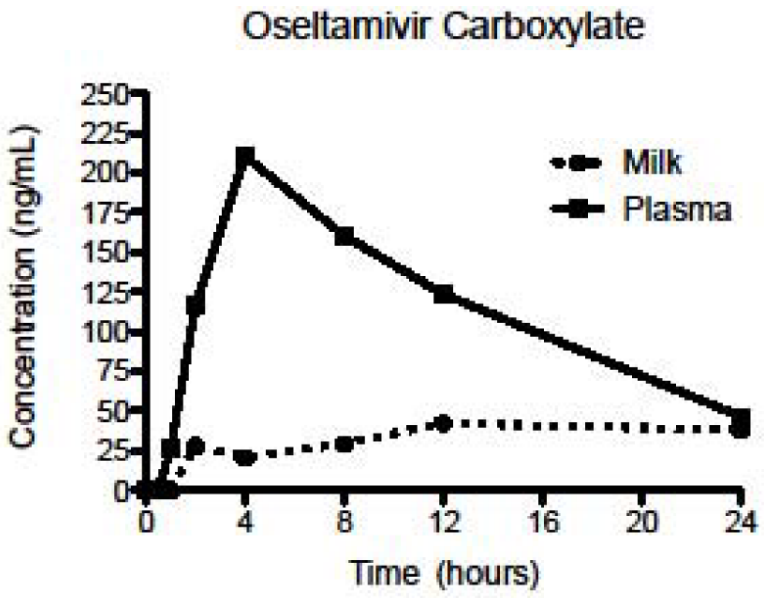

Figure 2.
Mean concentrations of oseltamivir carboxylate in plasma and breast milk after first dose.

Table 1

Pharmacokinetic parameters for oseltamivir phosphate prodrug and oseltamivir carboxylate in plasma and breast milk.

	OSELTAMIVIR PHOSPHATE		OSELTAMIVIR CARBOXYLATE	
	Plasma	**Breast milk**	**Plasma**	**Breast milk**
C_{max} (ng/mL)	70.1 ± 72.6	26.9 ± 14.0	224.3 ± 40.5	41.9 ± 21.0
T_{max} (hour)	2.6 ± 2.4	3.4 ± 2.2	4.6 ± 1.5	18.9 ± 6.4
$T_{1/2}$ (hour)	4.2 ± 2.4	4.2 ± 1.2	16.1 ± 8.0	n/a
$AUC_{0–24\ h}$ (ng·h/mL)	155.6 ± 57.9	143.4 ± 73.4	2611.7 ± 349.0	569 ± 405.8

Data reported as mean ± SD