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Pharmacokinetics of Oseltamivir According to Trimester of Pregnancy

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Abstract

Objective—To determine pharmacokinetic parameters for oseltamivir in all trimesters of pregnancy.

Methods—Thirty pregnant women, 10 per trimester, receiving oseltamivir phosphate 75 mg were recruited to study first-dose pharmacokinetics. Plasma samples were obtained at 0, 0.5, 1, 2, 4, 8, and 12 hours after the first dose. 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—There were no significant differences in the pharmacokinetics of oseltamivir by trimester except for an increased $T_{1/2}$ in the first trimester for oseltamivir phosphate and an increased C_{max} in the third trimester for oseltamivir carboxylate. The levels of oseltamivir carboxylate observed were within the range needed to achieve IC_{50} concentrations for pandemic H1N1.

Conclusion—The pharmacokinetics of oseltamivir do not change significantly according to trimester of pregnancy.

Keywords

Influenza; oseltamivir; pahrmacokinetics; pregnancy

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INTRODUCTION

Increased morbidity and mortality from influenza in pregnancy have been reported for seasonal and pandemic influenza, but the emergence of pandemic influenza A H1N1 in early 2009 heightened awareness of the dangers of influenza in pregnancy (1–2). Reports of pandemic influenza A H1N1 in pregnancy demonstrate that pregnant women are at increased risk for hospital admission, intensive care admission, death, and adverse neonatal outcomes (1, 3–10). In the United States, up to 5% of reported influenza-related deaths occurred in pregnant patients (7). Recognizing the increased risk of H1N1 influenza infection in pregnancy, the Centers for Disease Control and Prevention (CDC) recommended that all pregnant women with suspected influenza A H1N1 receive influenza antiviral treatment with oseltamivir and that pregnant women with close exposure to a person with H1N1 receive oseltamivir prophylaxis (10–11).

Oseltamivir is a neuraminidase inhibitor that is effective against both influenza A (including pandemic H1N1) and influenza B (12–13). The neuraminidase inhibitor binds to the active neuraminidase enzyme site, preventing enzymatic cleavage of the sialic acid bonds, and resulting in entrapment of newly replicated viruses on the host cell surface, thereby preventing progeny virion release. It also inhibits viral penetration into the respiratory tract epithelial cells (14, 15, 16). In healthy volunteers, oseltamivir 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 (17–19). Early data from the H1N1 pandemic suggest that prompt initiation of antiviral treatment in pregnant patients infected with influenza results in decreased risk of ICU admission and death (7).

There are no studies, however, to guide dosing of oseltamivir during pregnancy. Oseltamivir is absorbed by the gastrointestinal tract, rapidly hydrolyzed by hepatic esterases to the active metabolite oseltamivir carboxylase, and is excreted by the kidney through both glomerular filtration and secretion (14, 18). Given the physiologic changes of pregnancy that include a 50% increase in glomerular filtration rate and a 40–45% increase in blood volume (20), some investigators have advocated higher doses of oseltamivir in acutely ill pregnant patients with severe disease requiring ventilator support (21). In a meeting of experts convened by the CDC anticipating future pandemic influenza, however, Rassmussen and colleagues noted, “No data are available to address whether dosage adjustment is needed; thus, no dosage alteration for pregnant women are recommended at this time”(2). To provide some guidance on this issue, we studied the pharmacokinetics of first-dose oseltamivir in all trimesters of pregnancy in thirty pregnant patients with influenza or influenza exposure.

MATERIALS & METHODS

This study was approved by the Internal Review Board at the University of Texas Southwestern Medical Center, Dallas, Texas. Pregnant subjects with a singleton gestation, admitted to the hospital and receiving oseltamivir for treatment or prophylaxis of influenza were eligible for the study. In the 2008–2009 influenza season, only subjects who presented within forty-eight hours of symptom onset and who had a laboratory confirmed diagnosis of influenza were treated with antiviral therapy. During that influenza season, seasonal influenza A showed resistance to oseltamivir, and subjects with influenza A also received treatment with an M2 ion channel inhibitor (22). During the 2009–2010 H1N1 pandemic season, subjects were treated with oseltamivir based on clinically diagnosed and/or laboratory confirmed influenza and were treated regardless of time since symptom onset (11). In both influenza seasons, subjects being treated for influenza received oseltamivir phosphate (Tamiflu®) 75 mg capsule twice daily for five days. Pregnant subjects who were

hospitalized for other conditions, exposed to influenza, and elected to receive prophylaxis with oseltamivir were also eligible for the study. They received the approved adult influenza prophylaxis dosing of oseltamivir phosphate 75 mg orally once daily for ten days. Subjects were excluded if they had an allergy or prior adverse reaction to oseltamivir or known kidney or liver disease.

After the decision to treat had been made by the obstetrical team caring for the patient, the researchers were notified. Subjects who consented to participate in the study had blood samples drawn at the time of the first dose of medication and at 0.5, 1, 2, 4, 8, and 12 hours after the first dose of oseltamivir, for a total of seven blood draws. Plasma samples were separated and prepared for storage (−80° Celsius) for batch analysis.

Plasma 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 ng/mL and 10 ng/mL (RSD < 5%) for oseltamivir phosphate and oseltamivir carboxylate, respectively. Oseltamivir and oseltamivir carboxylate concentrations (ng/mL) were plotted versus time (hours) for each of the respective subjects. Data from the 30 subjects were analyzed both as a single group and as trimester subgroups. 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

Thirty-five subjects receiving oseltamivir were identified and approached for study participation, and thirty were enrolled. All but two patient were Hispanic (reflective of our patient population), and they ranged in age from 16–34 years (Table 1). Twenty-nine subjects were admitted with influenza: 13 with pandemic H1N1, 6 with 2008–2009 influenza B, and 10 with 2008–2009 Influenza A. One subject was admitted for gestational diabetes and elected prophylaxis for an influenza B exposure. All subjects received 75 mg oseltamivir phosphate capsules, and the subjects with 2008–2009 influenza A also received an M2 ion channel inhibitor (6 rimantidine/4 amantadine). All but subject number 11 had singleton gestations; she was enrolled in the study but was later determined to be ineligible due to a twin gestation. All but two study participants completed the seven scheduled plasma collections. Subject 4 elected to withdraw after four draws when her IV stopped working, and subject 21 did not have her 12-hour level analyzed because she received her second dose of medicine before the collection was completed. None of the subjects had severe influenza requiring mechanical ventilation or intensive care unit admission. The average BMI (kg/m^2) was in the class I obesity range (1^{st} trimester 30 ± 5, second trimester 33 ± 8, third trimester 30 ± 3), ranging from 21–48 kg/m^2. There was no significant difference in the BMI of subjects by trimester (p=0.282).

The pharmacokinetic pattern for oseltamivir was similar for each trimester (Figure 1). For oseltamivir, C_{max} (ng/mL) and T_{max} (hours) were not significantly different between trimesters, ranging from 80–101 ng/mL and 0.9–2.3 hours, respectively (Table 2). The half-life of oseltamivir ($T_{1/2}$) was significantly longer in the first trimester subjects (4.0 hours) compared with the second and third trimester subjects (2.1 and 1.5 hours, respectively). The $AUC_{0\text{-}12}$ (ng·hr/mL) was not significantly different between trimesters, ranging from 151 to 215 ng·hr/mL (Table 2).

For the active metabolite oseltamivir carboxylate, we also observed similar pharmacokinetics by trimester (Figure 2). The C_{max} (ng/mL) was significantly higher in the third trimester, 198 ng/mL, compared with those in the first and second trimester, 150 ng/mL and 153 ng/mL, respectively (Table 3). The $AUC_{0\text{-}12}$ (ng·hr/mL) was not significantly different between trimesters, ranging from 1828 ng·hr/mL in the first trimester to 2367 ng·hr/mL in the third trimester. The T_{max} and $T_{1/2}$ were not significantly different between trimesters and ranged from 3.4–4.6 hours and 6.4–9.4 hours, respectively.

COMMENT

Our study revealed several important observations: 1) the first-dose C_{max} for oseltamivir carboxylate in pregnancy were lower than the steady state C_{max} reported for non-pregnant subjects; 2) the levels of oseltamivir carboxylate observed were within the range needed to achieve IC_{50} concentrations for pandemic H1N1; 3) the $AUC_{0\text{-}12}$ for oseltamivir and oseltamivir carboxylate were within previously reported ranges for first-dose oseltamivir phosphate and did not differ among trimester.

Pregnancy does not appear to significantly affect the time to achieve maximum oseltamivir concentration. We observed values in pregnancy consistent with non-pregnant ranges (0.9–2.3 hours for oseltamivir and 3.4–4.6 for oseltamivir carboxylate). Similarly, the reported $T_{1/2}$ for oseltamivir is 1–3 hours (12, 15, 18) and for oseltamivir carboxylate is 6–10 hours (12, 14, 18), similar to our data. The $T_{1/2}$ of oseltamivir carboxylate was not different between trimesters and fell within the reported $T_{1/2}$ in non-pregnant subjects.

Pregnant subjects have similar first dose C_{max} for oseltamivir compared to non-pregnant subjects but may have lower C_{max} for oseltamivir carboxylate than reported values for non-pregnant subjects. The mean C_{max} (ng/ml) reported by the manufacturer for non-pregnant subjects receiving a 75 mg dose of oseltamivir phosphate is 65.2 ng/mL for oseltamivir and 348 ng/mL for oseltamivir carboxylate. (18) Brewster et al reported similar values of 75.1 ng/mL for oseltamivir phosphate and 276 ng/mL for oseltamivir carboxylate. (12) While the C_{max} we observed in pregnancy for oseltamivir is well within the prior reported ranges, the average C_{max} for the active metabolite in each trimester (150–198 ng/mL) was lower than previously reported values (18, 23).

Another important parameter regarding the concentration of oseltamivir carboxylate is the inhibitory concentration (IC). The concentration required *in vitro* to achieve a 50% or 90% inhibition of the neuraminidase enzyme is designated the IC_{50} or IC_{90}. The ICs vary by influenza type, subtype, strain, and clade. The manufacturer reports IC_{50} of 0.0008 μM to > 35 μM and IC_{90} of 0.004μM to > 100 μM for oseltamivir carboxylate (18). Other investigators have reported ICs that fall within this range, with influenza B generally having higher ICs (15, 24). The reported IC_{50} for pandemic H1N1 ranges from 0.28 to 1.41 nM (25). Based on our first dose C_{max} values, our subjects had average levels of 0.528 nM in the first trimester, 0.538 nM second trimester, and 0.697 nM third trimester. These values fall within the lower half of the range reported for H1N1. Specifically, the levels recorded in our study would meet the IC_{50} for approximately half of the strains reported (25). Considering H5N1 avian influenza, however, mean IC_{50} concentrations range from 0.09 to 11.45 depending on the H5N1 strain (26), which are above the levels we observed.

The $AUC_{0\text{-}12h}$ data are more complex. Although the $AUC_{0\text{-}12}$ was not different by trimester, the $AUC_{0\text{-}12}$ (and the C_{max}) for the active metabolite oseltamivir carboxylate was highest in the third trimester. This finding is surprising given the increasing blood volume, increasing GFR, and increasing placental unit in the third trimester, which led us to hypothesize that values would be lower during the third trimester compared to the first. The absence of a

decrease in levels in the third trimester may be because little oseltamivir or oseltamivir carboxylate reaches the amniotic cavity. Worley et al using an *ex vivo* placental model detected neither oseltamivir phosphate nor oseltamivir carboxylate in the transplacental perfusate when therapeutic dosing levels were used (27).

When comparing our $AUC_{0\text{-}12h}$ data in a pregnant population with influenza to previously published data in non-pregnant subjects, it is important to recognize that the levels in our study reflect first-day, first-dose pharmacokinetics. We found $AUC_{0\text{-}12h}$ for oseltamivir ranged from 151–215 ng·h/mL and for oseltamivir carboxylate ranged from 1828–2367 ng·h/mL. These values are within the means reported by Schentag et al for Caucasian (75.9 ng·h/mL and 1092 ng·h/mL, respectively) and for Japanese subjects (100 ng·h/mL and 1367ng·h/mL) following the first dose of oseltamivir phosphate (13). Similarly, He and colleagues calculated first dose $AUC_{0\text{-}12h}$ for 50 mg and 100 mg dosing and reported oseltamivir carboxylate levels of 1206 ng·h/mL and 2450 ng·h/mL, respectively (14). By comparison, the manufacturer reports the $AUC_{0\text{-}12h}$ for *steady state* after multiple 75 mg doses to be 112 ng·h/mL for oseltamivir and 2719 ng·h/mL for oseltamivir carboxylate. Schentag and He both reported first dose and steady state $AUC_{0\text{-}12h}$, and the steady state levels were approximately 1.5 times higher than the first dose $AUC_{0\text{-}12h}$ (12, 14). If this association is similar in pregnancy, our $AUC_{0\text{-}12h}$ at steady state would range from 2742 ng·h/mL first trimester to 3551 ng·h/mL third trimester, comparable with the $AUC_{0\text{-}12h}$ reported by the manufacturer.

Our study has several limitations. First, the study was designed to assess the pharmacokinetics only after the first dose of medication. We do not have antepartum steady state data, and comparisons of our observations with steady state IC_{50} data may not be valid. Second, we had a racially homogenous group. Limited data from prior studies, however, have not demonstrated racial differences in the pharmacokinetics of oseltamivir (13, 16). Finally, as other influenza strains emerge or oseltamivir resistance develops, IC concentrations for new strains should be considered in determining dosing and timing recommendations in pregnant and nonpregnant adults.

In conclusion, we found few significant differences in the pharmacokinetics of oseltamivir or oseltamivir carboxylate by pregnancy trimester. Furthermore, pregnancy did not appear to change significantly the timing of absorption or of conversion of oseltamivir phosphate to oseltamivir carboxylate. Concentrations of the active metabolite after the first dose were lower than non-pregnant first dose concentrations and lower than levels reported for steady-state concentrations in non-pregnant adults. These first-dose values may underestimate levels expected at steady state. Overall, we found that approved adult dosing of oseltamivir provides similar antepartum plasma concentrations to those achieved in non-pregnant subjects. This critical clinical evidence supports the current treatment recommendations for pregnant women with influenza.

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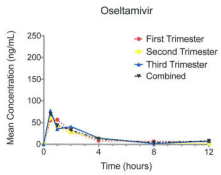

Figure 1.
Mean concentrations of oseltamivir after first dose graphed by entire cohort and by trimester.

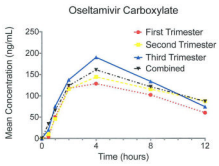

Figure 2.
Mean concentrations of oseltamivir carboxylate after first dose graphed by entire cohort and by trimester.

Table 1

Demographic data of individual patients including maternal age (years), gestational age (weeks), weight (pounds), BMI (kg/m^2), and influenza type.

Patient	Age	Gestational Age	Weight	BMI	Influenza Type
1	22	10–11	115	21	B
2	30	5–6	160	29	B
3	23	10–11	204	35	A
4	30	9–10	177	30	A
5	29	12–13	182	33	A
6	25	9–10	174	33	H1N1
7	16	9–10	182	36	H1N1
8	26	11–12	134	27	H1N1
9	21	10–11	169	30	H1N1
10	22	8–9	133	23	H1N1
11	33	18–19	165	29	A
12	23	16–17	153	26	A
13	31	21–22	264	48	B
14	25	21–22	153	27	A
15	21	18–19	169	33	H1N1
16	22	17–18	202	34	H1N1
17	26	25–26	162	34	H1N1
18	25	25–26	246	45	H1N1
19	30	22–23	120	26	H1N1
20	24	21–22	165	32	H1N1
21	20	32–33	193	37	B
22	20	34–35	176	34	B
23	27	28–29	150	28	A
24	25	37–38	218	36	Exposure
25	25	34–35	184	30	A
26	18	38–39	180	32	A
27	24	38–39	164	30	A
28	22	36–37	210	36	B

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Patient	Age	Gestational Age	Weight	BMI	Influenza Type
29	34	34–35	194	34	H1N1
30	26	34–35	166	32	H1N1

Table 2

Pharmacokinetic parameters for oseltamivir phosphate prodrug.

	Trimester 1	Trimester 2	Trimester 3	P-value
C_{max} (ng/mL)	80 ± 18	75 ± 56	101 ± 59	0.43
T_{max} (hour)	0.9 ± 0.5	1.1 ± 0.7	2.3 ± 3.6	0.30
$T_{1/2}$ (hour)	4.0 ± 3.1*	2.1 ± 0.8	1.5 ± 0.5	0.02
$AUC_{0–12\ h}$ (ng·h/mL)	215 ± 124	151 ± 57	166 ± 46	0.23

Data expressed as mean value with standard deviations.

* Trimester 1 is significantly different from Trimester 2 and 3.

Table 3

Pharmacokinetic parameters for active metabolite oseltamivir carboxylate.

	Trimester 1	Trimester 2	Trimester 3	P-value
C_{max} (ng/mL)	150 ± 23	153 ± 53	198 ± 43*	0.02
T_{max} (hour)	3.4 ± 1.0	4.6 ± 3.1	3.8 ± 1.8	0.46
$T_{1/2}$ (hour)	6.9 ± 2.3	9.4 ± 6.1	6.4 ± 1.5	0.23
$AUC_{0–12\ h}$ (ng·h/mL)	1828 ± 406	2325 ± 1008	2367 ± 650	0.269

Data expressed as mean value with standard deviations.

* Trimester 3 is significantly different from Trimester 1 and 2