Published in final edited form as:
Am J Obstet Gynecol. 2011 June ; 204(6 Suppl 1): S84–S88. doi:10.1016/j.ajog.2011.03.002.

Pharmacokinetics of Oseltamivir Among Pregnant and Non-pregnant Women

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Abstract

Objective—To delineate the pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate during pregnancy. Physiologic changes of pregnancy, including increased renal filtration and secretion, may increase the clearance of oseltamivir carboxylate.

Study Design—Sixteen pregnant women taking oseltamivir for prophylaxis or treatment of suspected/proven influenza infection were enrolled. Twenty-three non-pregnant reproductive-age females served as the control group. The primary pharmacokinetic endpoint was area under the plasma concentration-time curve (AUC) for oseltamivir carboxylate.

Results—Pregnancy did not alter the pharmacokinetic parameters of the parent compound, oseltamivir. However, for oseltamivir carboxylate the area under the plasma concentration-time curve (AUC) was significantly lower (p=0.007) and the apparent clearance significantly higher (p=0.006) in pregnant women compared with non-pregnant women.

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Conclusions—Pregnancy produces lower systemic levels of oseltamivir carboxylate. Increasing the dose and/or dosing frequency of oseltamivir during pregnancy may be necessary in order to achieve comparable exposure in pregnant and non-pregnant women.

Keywords

Influenza; Oseltamivir; Pregnancy; Treatment

Introduction

The recent 2009 H1N1 influenza pandemic reinforced the inevitability of novel influenza strains producing occasional pandemics [1]. Pregnant women represent a unique patient population that historically has been disproportionately affected by both seasonal and pandemic outbreaks of influenza. During the 20th century influenza pandemics, pregnant women with influenza were significantly more likely to suffer serious morbidity and have higher mortality rates than the general adult population [2-5]. This disproportionate morbidity has also been observed among pregnant women during seasonal influenza epidemics [2,6-8]. Furthermore, during the 2009 H1N1 influenza pandemic, higher rates of morbidity and mortality were reported among pregnant women with influenza compared to the general population, consistent with previous pandemics [9-11].

The primary antiviral agent that was stockpiled and subsequently used for both prophylaxis and treatment of 2009 H1N1 was oseltamivir (Tamiflu®). However, limited data exists to address the appropriate dosing regimen of this agent for pregnant women [2,12,13]. Despite this relative lack of specific information, the Centers of Disease Control and Prevention (CDC) recommended using standard adult dosing of oseltamivir for treatment of pregnant women with suspected or confirmed 2009 H1N1 influenza infection given the noted increased severity of disease and lack of apparent harm from treatment during pregnancy and lactation [14].

Pregnancy is known to result in numerous physiologic alterations that have the potential to dramatically affect the pharmacokinetics (PK), and subsequently concentrations of various therapeutic agents (15-17). Such alterations have been observed in absorption, metabolism, distribution and elimination of many classes of agents (18-21). In addition, sub-therapeutic antimicrobial drug levels in patients suffering from infectious diseases may contribute to lack of effectiveness and the development of drug resistance (22). Despite the known increased risk for untoward outcomes from influenza in pregnancy, no data exist to inform clinicians about the optimal dosing of oseltamivir in pregnancy. The goal of the current investigation was to characterize and compare the pharmacokinetics of oseltamivir in pregnant women and non-pregnant women.

Materials and Methods

Women were recruited from 3 clinical research centers in the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD) sponsored Obstetric-Fetal Pharmacology Research Units Network (OPRU). Sites include Magee-Womens Hospital of the University of Pittsburgh Medical Center, Pittsburgh, PA, University of Texas Medical Branch, Galveston, TX, and the University of Washington Medical Center, Seattle, WA. Pregnant subjects were recruited and enrolled during the 2009 influenza season from May 1, 2009 until December 31, 2010. All pregnant women were receiving oseltamivir either for prophylaxis or for treatment of proven 2009 H1N1 influenza or influenza-like-illness (ILI). The standard oral doses suggested for these indications are 75 mg once daily and 75 mg orally twice daily, respectively. Non-pregnant reproductive-age women took

oseltamivir only for the study and served as control subjects. All protocols were approved by each site's respective institutional review board (IRB) and all participants underwent the informed consent process using IRB-approved consent documents.

For all participants, demographic details as well as medical history and any concomitant medications used during the study period were collected. For pregnant women, gestational age, obstetric history, and pregnancy outcomes also were collected. All pregnant subjects were already on oseltamivir as prescribed for clinical purposes by their respective caregivers. Eligibility criteria for these women included: a) pregnant and on oseltamivir, b) 16 years of age or older, c) able to perform study procedures, and d) having a hematocrit of greater than 28%. For the non-pregnant cohort eligibility criteria included: a) age 18-50 years, b) willingness to participate, and c) lacking evidence of kidney or liver dysfunction (no elevations of either serum creatinine or AST/ALT levels) or significant anemia (hematocrit less than 28%) detected at the screening visit which took place within 5 working days of enrollment.

The pharmacokinetic study was performed in pregnant subjects after they had already been on oseltamivir for at least 48 hours. On the day of the study, serial blood samples were obtained just prior to the next scheduled dose and again over one dosing interval at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours (depending on the scheduled dosing regimen) after the dose. The non-pregnant women took a 48 hour course of 75 mg oseltamivir (either QD or BID) at home prior to reporting for study procedures. On the third day of therapy, the participants arrived at the clinical research site in the early morning after a 6 hour fast, underwent a pre-dose blood draw (trough), then took another 75 mg oral dose under direct observation by study staff. They subsequently underwent the same blood sampling protocol as the pregnant cohort.

Oseltamivir, oseltamivir carboxylate (the active mebolite), and the internal standards were extracted from K_3-EDTA/NaF or K_3-EDTA plasma samples by protein precipitation and the concentrations were determined by HPLC with tandem mass spectrometric detection. Detection was accomplished utilizing ion spray MS/MS in positive ion multiple reaction monitoring mode (MRM). The lower limit of quantification was 1.00 ng/mL with a calibration range up to 250 ng/mL for oseltamivir (parent drug) and the lower limit of quantification was 10.0 ng/mL with a calibration range up to 10,000 ng/mL for oseltamivir carboxylate (active metabolite). For the analysis of urine samples, the analytes and the internal standards were isolated from urine samples by dilution and determined by HPLC with tandem mass spectrometric detection. Detection was accomplished utilizing ion spray MS/MS in positive ion multiple reaction monitoring mode (MRM). The lower limit of quantification was 5.0 ng/mL with a calibration range up to 1000 ng/mL for oseltamivir and the lower limit of quantification was 30.0 ng/mL with a calibration range up to 30,000 ng/mL for oseltamivir carboxylate. All the samples were assayed by PRA International (Early Development Services, Westerbrink 3, 9405 BJ Assen, The Netherlands).

Non-compartmental analysis was performed and various pharmacokinetic parameters were generated using WinNonlin software (version 4.1; Pharsight Corporation, Mountainview, CA). The half life ($t_{1/2}$) of oseltamivir and oseltamivir carboxylate was calculated from the terminal disposition phase using at least three data points. In each of the participating subjects the area under the plasma concentration-time curve (AUC) for oseltamivir and oseltamivir carboxylate for the study dose (0-end of dosing interval) was calculated using reverse superposition principle. The apparent clearance of the parent drug was calculated as dose/AUC. The apparent clearance of oseltamivir carboxylate was calculated as dose of oseltamivir × 0.91 (corrected for molecular weight) / AUC of oseltamivir carboxylate. The

apparent volume of distribution of oseltamivir (Vz/F) during the terminal disposition phase was calculated from apparent clearance and half life.

The pharmacokinetic parameters and demographic data were compared between pregnant and non-pregnant subjects using a two-tailed Student *t*-test or non-parametric analytical methods where appropriate (depending on normality of distribution). A p value of <0.05 was considered statistically significant.

Results

A total of 26 pregnant women were approached for participation and 22 underwent the informed consent process. Six pregnant women opted for non-participation for various reasons after undergoing informed consent procedures. There were zero non-pregnant women that underwent informed consent that subsequently decided not to participate. Data from 16 pregnant women and 23 non-pregnant control women were available for analysis.

The demographic characteristics for the two study populations are listed in Table 1. Of note, pregnant women were slightly younger, had higher body mass index (BMI) values and higher values for creatinine clearance than controls. Among the 16 pregnant women, 3 were in the first trimester, 9 in the second, and 4 in the third. Fourteen of the 16 (88%) were receiving oseltamivir as a treatment regimen for suspected or proven influenza, and the remaining 2 (12%) were on once daily prophylaxis after exposure to influenza. For the treatment group (N=14), 12 patients were receiving the standard 75 mg twice daily regimen and 2 were taking it three times daily. All dosage regimens were selected at the discretion of the prescribing physician and not altered for study purposes. During the pharmacokinetic sampling times, no pregnant participants reported any adverse events related to the ingestion of oseltamivir at the doses administered (including no complaints of gastrointestinal upset). Eight of the 23 (35%) non-pregnant control subjects complained of mild stomach upset and nausea. No other complaints related to drug tolerance were noted in either cohort.

For the pregnant subjects, 9 of the 16 (56%) had polymerase chain reaction (PCR) proven influenza A, all presumed to be 2009 H1N1 given corresponding local disease epidemiology. The remaining 7 pregnant subjects either had negative testing or no testing performed. Of the 14 pregnant subjects on a treatment regimen, 7 (50%) were hospitalized for at least 23 hours in the management of their influenza-like illness and the other half were managed as outpatients. One of the hospitalized pregnant subjects was temporarily cared for in the intensive care unit, subsequently improved, and discharged from the hospital. She subsequently delivered distant in time from the influenza-related hospitalization. None of the pregnant subjects died during the course of the study.

In terms of pregnancy outcomes, data is available for analysis from 14 of 16 (87.5%) participants. Two of 14 (14.2%) delivered prematurely, both at 31 weeks of gestation. One of these subjects had a confirmed + influenza A PCR, however, it is unclear if the delivery was related to influenza infection. The remaining 12 (85.8%) delivered at or beyond 37 weeks of gestation (term). All babies with birth outcomes available had 5 minute apgar scores of ≥ 8, and the range of birthweight for all term babies was 2,600-4,440 g. None of the babies delivered at term were admitted to the neonatal intensive care unit.

The non-compartmental pharmacokinetic parameters for pregnant and non-pregnant subjects are summarized in Table 2. The plasma concentration vs. time profile for oseltamivir was not different between the pregnant and non-pregnant subjects. The AUC of oseltamivir carboxylate for the 75 mg dose of oseltamivir was on an average 30% lower in pregnant woman than in non-pregnant women ($p \leq 0.007$). In general with the dosing regimens used, the maximum concentration achieved after dosing (C_{max}) was significantly higher in non-

pregnant women. The apparent oral clearance for oseltamivir carboxylate was also significantly higher in pregnant subjects (p=0.006). The apparent half-life ($t_{1/2}$) did not differ significantly between the two groups. There was a poor correlation (r = 0.25) between creatinine clearance and the apparent clearance of oseltamivir carboxylate in all subjects.

Discussion

This study demonstrates that exposure to oseltamivir carboxylate (active metabolite of oseltamivir) following oral administration of oseltamivir is decreased by approximately 30% during pregnancy compared to non-pregnant women of reproductiveage. While the precise clinical implications of these findings are not completely understood, this information is important and could have a substantial impact on dosing recommendations and antiviral effectiveness in pregnant women with influenza. The pharmacokinetic alterations are of particular concern for pregnant women given the reproducible and disproportionate morbidity noted during seasonal influenza epidemics and occasional pandemics, including the recent 2009 H1N1 experience (2-11).

Oseltamivir is well absorbed and is rapidly converted to the active metabolite by carboxylesterase-1 (primary elimination pathway). Less than 5% of the administered dose is excreted in the urine unchanged. The similarity in the pharmacokinetic parameters of the parent drug oseltamivir in pregnant and non-pregnant subjects suggests similar activity of carboxylesterase-1 in the pregnant and non-pregnant groups. In contrast, the predominant route of elimination of oseltamivir carboxylate is through the kidney. Oseltamivir carboxylate is filtered and secreted via organic anion transporter (OAT) 1 (23). The findings of significantly lower oseltamivir carboxylate concentrations in pregnant women are not unexpected. The difference in plasma concentrations is predictable because renal function (creatinine clearance and renal plasma flow) is greater in pregnant than in non-pregnant women. It is also possible that the activity of OAT may be altered during pregnancy.

The potential implications of these findings in terms of dosing and efficacy in pregnancy warrant attention and further validation with a larger sample size. The relationship between systemic levels of oseltamivir carboxylate and *in vivo* clinical antiviral activity among influenza infected patients (pharmacodynamics, PD) is poorly characterized and has not been established (24). Recently, an *in vitro* model system has identified the variable "AUC_{24} :IC50" as a new potential efficacy endpoint that may allow for better PD approximations (25). While this new variable is theoretical, it may assist in indirect PD approximations of dosing and there is no implicit reason to believe such an association would be altered by pregnancy, although this presumption has not been evaluated. Despite the lack of *in vivo* correlation, it is recognized that the standard dosing regimen of 75 mg orally twice daily in non-pregnant adults generally produces serum concentrations that are well above the level required to inhibit viral replication. The 50% inhibitory concentrations (IC_{50}) for sensitive influenza virus strains are 0.01-69.2 ng/ml (23,24,26). However, higher IC_{50} values have been reported for some influenza strains noted to demonstrate resistance to neuraminidase inhibition (24,27). Individual variations in metabolism, renal function and other variations in physiologic parameters affecting the elimination of drugs in pregnancy may alter individual drug exposure. Such changes in drug exposure could render standard dosing in pregnancy inadequate for effectiveness and potentially create an environment conducive for the development of viral resistance.

It has been demonstrated that oseltamivir has a very wide margin of safety when used in doses much higher than what are currently recommended (28). It has been recently demonstrated that doses as high as 450 mg twice daily (6 fold increase from standard dosing) were well tolerated by nearly 200 volunteer study subjects with no clear correlation

between adverse events and dose. This referenced investigation was undertaken with the intention to justify future higher doses for critically ill individuals. While this has not been studied in pregnancy, it does appear that modest increases in the dose would be well tolerated. Although we do not currently have adequate data to firmly establish pregnant treatment dosing guidelines, an increase in dose (from 75 mg twice daily to 75 mg three times a day) may be warranted during pregnancy in an attempt to better approximate comparable drug exposure in non-pregnant subjects. This could be done with a reasonable level of confidence in maternal tolerance of the higher dose. It must be remembered however that no clinical data exists to validate this suggestion at this time.

The importance of timely oseltamivir therapy (begun within 48 hours of symptom onset) has been advised by the manufacturer and has been clinically validated via emerging data from the 2009 H1N1 pandemic [10]. As noted by these investigators, initiation of therapy greater than 48 hours after disease onset has been linked with worse maternal course of disease as evidenced by higher rates of ICU admission and death. However, the issue of dose and relation to clinical outcomes has not been addressed previously. During the recent influenza pandemic many clinicians empirically increased the dose of oseltamivir in critically ill patients (non-pregnant as well as pregnant) without a robust evidence base. Given the findings, future investigations addressing changes in dosing regimens (shortened dosing intervals, increased doses, or a combination) in pregnancy should be a top priority.

There are several limitations to this report that warrant attention. While the presence of a control population of non-pregnant reproductive-age women to compare against the pregnant women's data is a key strength of this study, the noted differences in demographics between the 2 groups could be relevant in regards to pharmacokinetic profiles (age, race, body mass index). Given the relatively small sample size, we were unable to definitively investigate the contributions of the covariates mentioned above. However, we believe that given the life threatening nature of H1N1 infection during pregnancy and the upcoming/ current influenza season(s), it is essential to report the currently available information. Additional recruitment to increase sample size and potentially minimize these demographic differences is underway to validate the current results and make them more widely applicable. Finally, this study did not address the impact of gestational age on the clearance of oseltamivir carboxylate. Future studies should evaluate whether the clearance of oseltamivir carboxylate differs by trimester. An evaluation of the potential exposure of the fetus to oseltamivir and oseltamivir carboxylate is also important.

Despite these limitations we conclude that the pharmacokinetics of the active metabolite of oseltamivir is affected by pregnancy. Accordingly, caregivers of pregnant women may consider increasing the dose of oseltamivir to 75 mg three times daily when treating influenza infection during pregnancy. Such a dosing regimen would not only provide a higher drug exposure but also a higher trough level of the active metabolite. Higher dose or dosing frequency to attain sustained high-level metabolite exposure may theoretically be especially important for critically-ill pregnant women due to ongoing viral replication in different tissue compartments other than blood. Clinical validation of our preliminary observation warrants further investigation given the importance of appropriate antiviral treatment among this uniquely vulnerable patient population.

Acknowledgments

The study team acknowledges Roche Pharmaceuticals for sample analysis and logistic support.

This work was supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (HD047905, HD047891, HD047892), and by the Office of Research on Women's Health, NIH. DRM was supported by funds from the intramural program of NICHD, NIH. In addition, this work was supported in part

by grant #UL1RR025014 from the NIH National Center for Research Resources. The contents of this paper are the views of the authors and do not necessarily represent the official view of *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Office of Research on Women's Health, or National Institutes of Health.

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Table 1
Demographic and Clinical Characteristics of Participants

Characteristic	Pregnant (N=16)	Non-pregnant Control (N=23)	P *
Median Age (years)	23.2 (range 18-40)	32.0 (range 19-50)	**0.007**
Race			**<0.001**
Caucasian	7	23	
African American	9	0	
Body weight (kg)	88 (59-147)	71 (52-112)	**0.006**
Median BMI	29.3 (range 24.2-49.5)	27.6 (range 19.4-37.8)	**0.04**
Creatinine Clearance (ml/min)	172 (range 52-327)	120 (69-189)	**0.002**
Mean Gestational Age (weeks)	24.6 (range 9.7 – 36)	NA	

* Using Student's T-test or 2-Sample test for proportions where appropriate

Table 2

Estimated Pharmacokinetic Parameters

Parameter	Oseltamivir Pregnant	Oseltamivir Non-Pregnant	P value	Oseltamivir carboxylate Pregnant	Oseltamivir carboxylate Non-Pregnant	P value
AUC* (ng/ml/hr)	164 (+51)	157 (+54)	0.88	3460 (+1350)	4719 (+1263)	**0.007**
CL/F** (L/hr)	501 (+160)	543 (+225)	0.50	24.5 (+8.4)	17 (+4.7)	**0.006**
V_Z/F*** (L)	2108 (+1366)	1768 (+1445)	0.46			NA
$T_{1/2}$ ± (hr)	3.1(+2.1)	3 (+4.1)	0.94	6.2 (+1.6)	7.1 (+1.9)	0.13

*Area under the plasma concentration-time curve

**Apparent oral clearance

***Apparent volume of distribution

±Apparent Half-life