An Observational Study on the Pharmacokinetics of Oseltamivir in Lactating Influenza Patients

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Influenza infection may lead to serious complications in the postpartum period, therefore, oseltamivir treatment in these patients and their breastfed infants is of great importance. However, the pharmacokinetics of oseltamivir in postpartum lactating women with acute influenza infection, and the consequent infant exposure to oseltamivir are still unknown, and these data would help in assessing risk and the need for dose adjustment in breastfed infants. Six lactating women with influenza-like symptoms, at a standard dose of 75 mg oral oseltamivir twice daily for 5 days, were recruited in this phase IV clinical study during the 2011/2012 H1N1 pandemic seasons. Breast milk/colostrum and venous blood samples were taken at multiple timepoints, maternal urine samples were obtained from total output within the 12-hour observational period following the seventh dose of oseltamivir. Oseltamivir phosphate (OP) reached a maximum 69.5 ± 29.4 ng/mL concentration in breast milk, higher than that found in the plasma, and showed elimination within ~8 hours. Oseltamivir carboxylate (active metabolite of OP) showed a lower, nearly steady-state concentration in breast milk during the observational period (maximum plasma concentration (C_{max}) = 38.4 ± 12.9 ng/mL). Based on estimated daily milk consumption of exclusively breastfed infants, their calculated daily exposure is < 0.1% of the infant dose of oseltamivir for treatment of influenza as per marketing authorization. Here, we provide the first maternal breast milk pharmacokinetic data for oral multiple-dose oseltamivir in lactating patients with influenza and showed that its concentration in the breast milk is not sufficient to reach a therapeutic dose for breastfed infants.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Oseltamivir is a neuraminidase inhibitor for the treatment of influenza. Both oseltamivir phosphate and oseltamivir carboxylate are secreted into breast milk, however, there are limited data available on the pharmacokinetics of oseltamivir in postpartum patients and the potential exposure for their infants to the drug.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study evaluated the pharmacokinetic parameters of oseltamivir in breast milk of lactating, patients with influenza and the potential exposure of exclusively breastfed infants to oseltamivir to provide dosage recommendations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ This study provided the first maternal breast milk pharmacokinetic data for oral, multiple-dose oseltamivir in breastfeeding patients with influenza. Oseltamivir is secreted in the breast milk of patients with influenza, however, its concentration in the breast milk does not reach a therapeutic dose for exclusively breastfed infants.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study demonstrates that oral oseltamivir therapy of lactating patients with influenza does not influence the dosage recommendations for their infants who are at high risk for acquiring infection.

Pregnancy is associated with an increased risk of adverse outcomes, hospitalization, and mortality from influenza infection compared with the non-pregnant adult population. The most common complication is pneumonia, which frequently occurs in high-risk patients, including pregnant and postpartum women.[1,2] Pregnant women with severe influenza are more likely to deliver preterm

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and low-weight infants.[3] Antiviral treatment of documented or suspected influenza is recommended to be started immediately in pregnant and up to 2-weeks postpartum women irrespective of their previous vaccination.[4]

Newborns and infants infected with influenza virus are at great risk of severe disease and hospitalization, usually with symptoms of fever, otitis media, pneumonia, or croup.[5–7] The transmission of most viruses through breast milk to infants is rare.[8] For women diagnosed with perinatal influenza, the infection risk for their newborn may be reduced by paying attention to hand hygiene, whereas antiviral treatment may also be protective.[9,10] If possible, breastfeeding should not be discontinued because it is the first line protection of infants against infectious diseases.[8,11] In addition, prenatal and postpartum maternal vaccination decreases the risk of influenza infection and influenza-related hospitalization among infants.[12] Vaccines are currently not available for young infants, however, the antiviral drug oseltamivir can be used to reduce the clinical impact of multiple types of influenza without major adverse effects.[13,14]

Oseltamivir, approved under the trade name Tamiflu, is a neuraminidase inhibitor (NAI), that targets influenza-infected cells and blocks virion release.[15] For the treatment of both influenza A and B, oseltamivir is the most frequently prescribed NAI.[16] The NAIs effectively reduce influenza-related complications, especially in high-risk patients, and mortality among hospitalized patients.[17] The most common adverse events associated with NAIs include nausea and vomiting.[17] Oseltamivir treatment in adults and children, including infants with influenza-like symptoms, was approved by the European Medicines Agency (EMA).[18] Following absorption of the prodrug, oseltamivir phosphate (OP), there is extensive conversion to its active metabolite, oseltamivir carboxylate (OC), by hepatic esterases. Elimination is in the urine in its active form.[18]

The EMA released a guideline in 2009, describing the need for clinical trials in pregnant and lactating women.[19] Currently, there are very limited data available on the use of oseltamivir by breastfeeding women or on excretion of oseltamivir or its active metabolite in breast milk.[20,21] In a study by Greer *et al.*,[21] the pharmacokinetics of oseltamivir in breast milk was studied in 7 healthy women within 48 hours of delivery, where they found that OC was present at low concentrations in breast milk. However, currently, there are no data on the maternal breast milk pharmacokinetics of oseltamivir in breastfeeding patients with influenza. Thus, it is challenging to determine the appropriate dosage of antiviral treatment for breastfeeding infants born to infected mothers, who are at risk of acquiring influenza infection. Here, we investigated the maternal breast milk pharmacokinetics of OP and its active metabolite, OC in postpartum lactating patients with influenza, and the potential exposure of exclusively breastfed infants to oseltamivir to provide dosage recommendations.

METHODS

Study design

This phase IV clinical trial was conducted in two investigation sites, the Department of Obstetrics and Gynecology at University of Debrecen, Debrecen, Hungary, and the Department of Obstetrics and Gynecology at Selye János Hospital, Komárom, Hungary. The study protocol was approved by the National Institute of Pharmacy (NIP) on April 16, 2010, approval number: OGYI/12342-6/2010, approval number of amendment decision: OGYI/49198-4/2011, and by the Ethics Committee for Clinical Pharmacology of Medical Research Council, approval number: 1998-0/2010-1017EKL, approval number of amendment decision: 312424-0/2012-EKL. The study is registered in the clinicaltrials.gov database (NCT01130636), titled An Observational Study on the Pharmacokinetics of Oseltamivir in the Treatment of Influenza During Lactation, Phase IV Trial. The sample collections were carried out during the pandemic seasons in 2011 Q1 and 2012 Q1. Analytical measurements were carried out between September 28 and October 2, 2012, by BASi Laboratory (West Lafayette, IN).

White, breastfeeding patients or women who had just given birth, aged 18 years and older, diagnosed with influenza were eligible for the study. The patients were excluded from participation if (i) any of the β-HCG blood test, β-HCG urine test or ultrasound examination provided a positive result, (ii) there was suspicion of infection with bacteria or a respiratory virus other than influenza, (iii) they had known or suspected immunosuppression, (iv) they had an allergy or prior adverse reaction to oseltamivir, or (v) had a history of uncontrolled seizures, central nervous system disorders, or psychiatric disability. All recruited patients signed a written informed consent form.

Patients received oseltamivir (Tamiflu hard capsules, provided by Roche, Nutley, NJ) at a standard dose of 75 mg twice daily for 5 days. On the fourth day of oseltamivir treatment, when plasma concentrations of both oseltamivir and its active metabolite are expected to be at steady-state,[22] patients were admitted for a 12-hour period to enable collection of breast milk, blood, and maternal urine samples. Maternal peripheral venous blood was collected immediately before the first dose and 2.5 hours after the first dose of medication (seventh dose of oseltamivir treatment). Blood samples were processed to separate plasma and stored in fluoride/EDTA tubes at −80°C for further analysis. Breast milk/colostrum samples were obtained at 0, 1, 2, 4, 6, 8, 10, and 12 hours following the daily first dose (seventh dose of oseltamivir treatment), and stored in fluoride/EDTA tubes at a temperature not exceeding −70°C until use. Maternal urine samples were obtained from total urine output within the 12-hour observational period and stored at a temperature not exceeding −70°C (**Figure 1**). Although the study was not powered to further assess differences between subgroups, we also analyzed OP and OC concentrations in colostrum ($n = 3$, < 7 days after giving birth, according to Ballard and Morrow, 2013)[23] and breast milk ($n = 3$, more than 7 days after giving birth) separately.

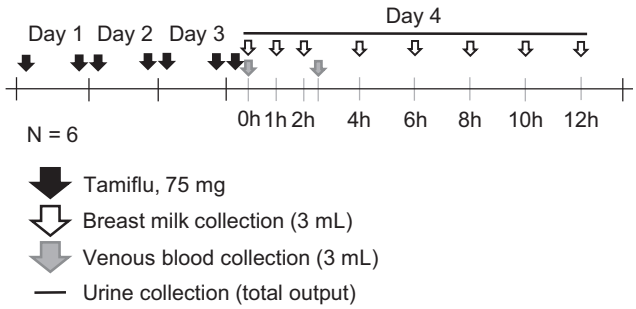

Figure 1 Breast feeding patients ($n = 6$) with diagnosed influenza were indicated for oseltamivir treatment at a standard dose of 75 mg twice daily. On the fourth day of oseltamivir treatment, the patients were admitted for a 12-hour period to enable collection of pharmacokinetic specimens. Then, 3 mL of breast milk and venous blood were collected at given timepoints, whereas total maternal urine output was collected throughout the 12-hour period.

Analytical measurements

Plasma, breast milk, and maternal urine samples were analyzed at the BASi Laboratory for OP and OC content using the tandem mass spectrometric method. OP and OC were extracted by protein precipitation from breast milk, EDTA-plasma, and urine samples. Before extraction, oseltamivir-d3 and oseltamivir acid-d3 were added as internal standards. After centrifugation, the supernatant was collected, evaporated to dryness, then reconstituted with 100 µL of water, and injected into an liquid-chromatography tandem mass spectrometry using a Kinetex PFP analytical column with an acetonitrile/water/formic acid mobile phase. Salt forms of the reference standards, OP and OC acid tartrate hydrate were received and used. Correction factors were applied to obtain the free base of the analytes. The lower limit of quantification for the assay was 10 ng/mL, the upper limit was 10,000 ng/mL. The concentrations of the study samples were reported as free bases of OP and OC acid.

Average consumption calculation for infants

Area under the curve (AUC) was calculated using the linear trapezoidal rule. AUC_{0-12} provides an index of the total systemic exposure to the drug and metabolite over the 12-hour observational period, and its appearance in breast milk/colostrum and likely exposure to nursing infants. The average concentration of OP or OC in breast milk was calculated based on the following equation[24]:

$$C_{\text{breast milk,av}}\left(\text{ng/mL}\right) = AUC_{\text{breast milk 0–12h}}\left(\text{ng/h/mL}\right)/12\,\text{h}. \quad (1)$$

Table 1 The age and number of days between parturition and sample collection for each patient

Subject #	Age (years)	Number of days between partum and sample collection
201	34	4
202	27	5
301	36	13
302	31	5
303	30	69
304	33	107
Mean	31.8	33.8
SEM	1.3	17.9

The daily dose of oseltamivir for infants was estimated based on the average oseltamivir concentration in breast milk and estimated daily breast milk consumption of exclusively breastfed infants[25]:

$$\text{Infant dose}\left(\text{ng/kg/day}\right) = C_{\text{breast milk av}}{}^{*}\ 150\,\text{mL/kg/day}. \quad (2)$$

Statistical analysis

The breast milk/colostrums, plasma, and maternal urine concentrations of OP and OC were plotted to generate plasma and breast milk concentration time curves as appropriate. For OP and OC, kinetic parameters were estimated from the plasma and breast milk concentration time curves. The differences in concentrations of OP or OC between breast milk and colostrum samples was analyzed by two-way analysis of variance.

RESULTS

Six White women who were breastfeeding or had just given birth and had been diagnosed with influenza were enrolled in the present study. Three patients were within 5 days of giving birth at the time of sampling, and 3 patients were 13 days postpartum (**Table 1**). The ages of the 6 patients ranged from 27 to 36 years (**Table 1**). The patients were prescribed 75 mg of OP orally twice daily. On day 4 of oseltamivir therapy, patients were enrolled for a 12-hour period for sample collection.

The pharmacokinetic parameters of both OP (**Table 2**) and its active metabolite OC (**Table 3**) were observed in breast milk samples. As shown in **Figure 2**, both OP and OC were found in breast milk, plasma, and maternal urine samples. Maximal concentration (C_{max}) of OP was 69.5 ± 29.4 ng/mL in breast milk, which is higher compared to that found in the maternal plasma at 0 and 2.5 hours (3.3 ± 0.6 ng/mL and 25.5 ± 3.4 ng/mL, respectively; **Figure 2a**). Reaching the C_{max} of OP in breast milk was 1.33 ± 0.52 hours. Elimination of OP from breast milk occurred 8 hours after the seventh dose of oseltamivir treatment. The half-life of OP in breast milk was 2.11 ± 0.451 hours. The mean concentration of OP in maternal urine samples was 2.05 ± 0.410 µg/mL during the total 12-hour long observational period (**Figure 3**).

The C_{max} of OC was 38.4 ± 12.9 ng/mL in breast milk, which is ~10-times lower compared with plasma concentrations (245.8 ± 21.5 ng/mL at 0 hours and 354.8 ± 34.0 ng/mL at

Table 2 Pharmacokinetic parameters for oseltamivir phosphate prodrug in breast milk

	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-12h} (ng/h/mL)	AUC_{0-INF} (ng/h/mL)	Half life (h)
N	6	6	6	6	6	6
Mean	69.5	1.33	2.17	235	242	2.11
SD	29.4	0.52	0.73	78.2	79.4	0.45
Min	40.9	1.00	1.50	153	157	1.51
Median	60.0	1.00	1.90	223	230	2.08
Max	111.0	2.00	3.30	372	380	2.83
CV% mean	42.3	38.70	33.70	33.2	32.8	21.40
Geometric mean	64.6	1.26	2.07	225	232	2.07
CV% geometric mean	43.4	37.00	33.00	32.2	32.0	21.60

AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV%, coefficient of variation percentage; T_{max}, time of maximum plasma concentration.

Table 3 Pharmacokinetic parameters for oseltamivir carboxylate in breast milk

	C_{max} (ng/mL)	T_{max} (h)	C_{min} (ng/mL)	AUC_{0-12h} (ng/h/mL)	AUC_{0-INF} (ng/h/mL)	Half life (h)
N	6	6	6	6	6	6
Mean	38.4	5.33	24.3	382	878	12.50
SD	12.9	1.63	10.8	156	305	3.76
Min	26.8	4.00	11.5	215	471	9.74
Median	33.8	5.00	23.1	361	847	10.80
Max	63.3	8.00	43.1	678	1,280	19.40
CV% Mean	33.5	30.60	44.5	40.9	34.8	30.10
Geometric mean	37.0	5.14	22.4	360	831	12.10
CV% geometric mean	29.8	30.00	46.6	38.6	38.4	27.30

AUC, area under the curve; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CV%, coefficient of variation percentage; T_{max}, time of maximum plasma concentration.

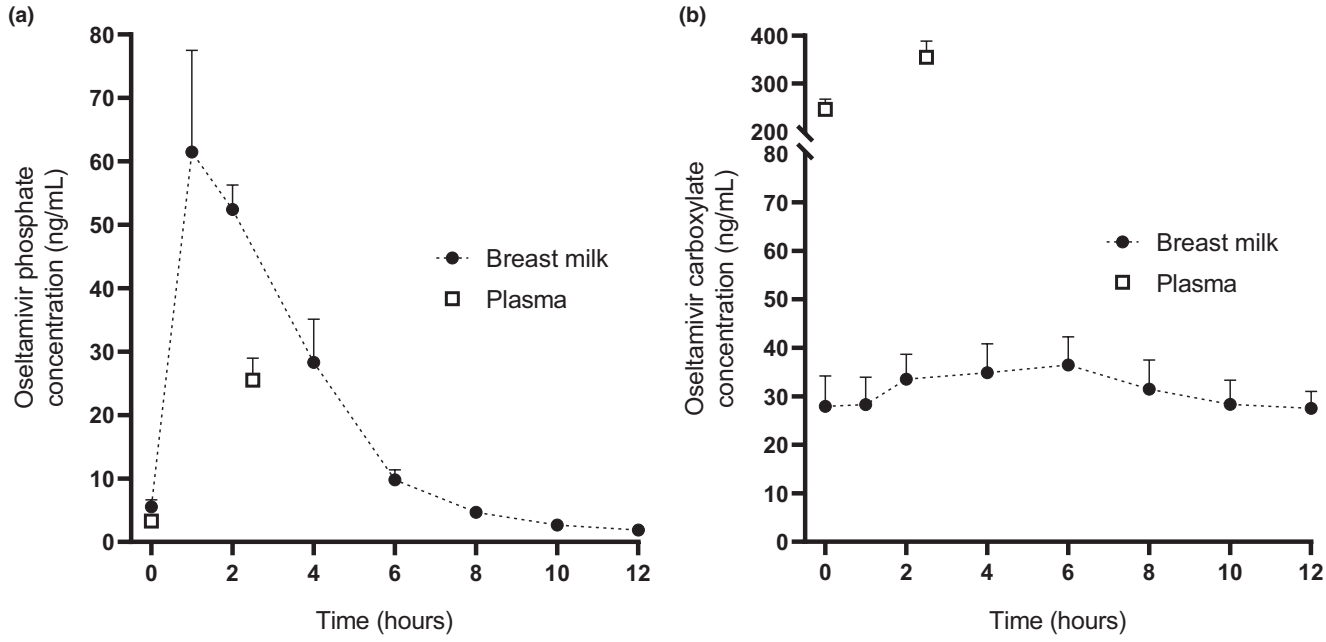

Figure 2 (a) Mean concentrations of oseltamivir phosphate in breast milk and plasma. (b) Mean concentrations of oseltamivir carboxylate in breast milk and plasma. Data are shown as mean ± SEM, $n = 6$.

2.5 hours; **Figure 2b**). Reaching the C_{max} of OC in breast milk was 5.33 ± 1.63 hours, which is longer than that of OP. OC was detected in the breast milk throughout the observational period. The half-life of OC in breast milk was 12.5 ± 3.76 hours, which is higher than that of OP. The mean concentration of OC in maternal urine samples was 50.75 ± 9.695 µg/mL during the 12-hour observational period (**Figure 3**).

Although the study was not powered to measure colostrum and breast milk separately, we have shown the data separately regarding the concentrations of OP and OC (**Figures S1** and **S2**). These data show no significant difference in the pharmacokinetics of OP and OC between breast milk and colostrum.

Based on the measured oseltamivir concentrations in the breast milk, the average concentrations were calculated to estimate the daily exposure to oseltamivir for exclusively breastfed infants based on their daily milk consumption. The average concentration of OP and OC were 19.58 and 31.83 ng/mL, respectively. The calculated daily exposure to OP and OC was 2.94 and 4.77 µg/kg/day, respectively, for exclusively breastfed infants, which is < 0.1% of the recommended therapeutic dose for 0 to 12 months old infants (3 mg/kg twice daily) according to the summary of product characteristics of Tamiflu hard capsules.[18]

DISCUSSION

Herein, we investigated the pharmacokinetics of OP and its active metabolite, OC, in plasma and breast milk in postpartum patients with influenza and provided the first multidose, maternal breast milk pharmacokinetic data for oral multiple-dose oseltamivir in lactating patients with influenza. Moreover,

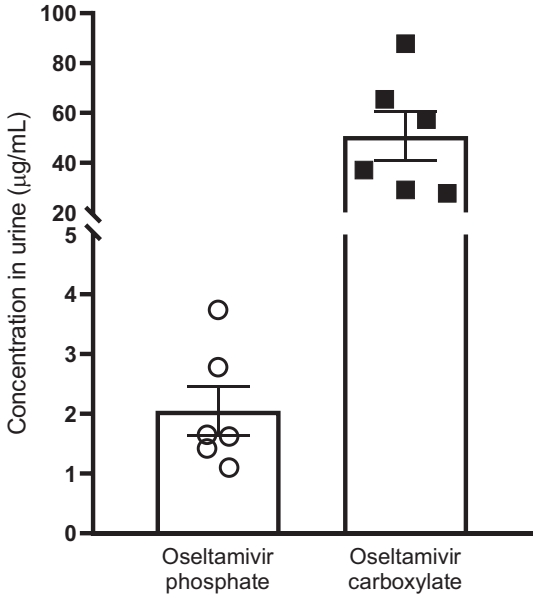

Figure 3 Cumulative concentrations of oseltamivir phosphate and oseltamivir carboxylate after 12 hours of maternal urine collection. Data are shown as mean ± SEM, $n = 6$.

we demonstrated for the first time, that based on the estimated daily consumption of breast milk by exclusively breastfed infants, the average daily oseltamivir exposure from breast milk is not sufficient to reach a therapeutic dose of oseltamivir for infants (3 mg/kg twice daily).

In our present study, we analyzed the pharmacokinetic parameters of OP and OC in postpartum influenza patients with a regular dosage of 75 mg oseltamivir twice daily. The concentration of the prodrug oseltamivir phosphate was higher in breast milk compared with plasma, whereas the converse was true for the metabolite. The higher concentration of OP in breast milk compared with plasma as opposed to OC is not surprising given the higher lipophilicity of the prodrug compared with the metabolite and the relatively high lipophilicity of breast milk compared with plasma.[26,27] The C_{max} of OP in the breast milk in our study was 69.5 ± 29.4 ng/mL. In comparison, in a previous study, Greer *et al*. reported that in healthy postpartum subjects, following a single dose of oseltamivir (75 mg), the C_{max} of OP was 26.9 ± 14.0 ng/mL in the breast milk.[21] Influenza infection was previously reported not to affect the pharmacokinetic parameters of oseltamivir compared with healthy subjects.[28] Thus, the higher concentration of OP in the breast milk in our study compared with Greer *et al*. could be explained by the prolonged repeated dose treatment of patients with influenza for 3 days. For OC, we found a C_{max} (38.4 ± 12.9 ng/mL) comparable to that found previously in the breast milk of healthy subjects (41.9 ± 21.0 ng/mL).[21] In a case report of an influenza-infected, lactating woman, the steady-state concentration of OC in the breast milk was also comparable to that found in our study.[20] The time required to achieve the C_{max} of both OP and OC in breast milk was shorter in our study than that previously reported in healthy postpartum subjects. The half-life of OP was 4.2 ± 1.2 hours in healthy subjects, which is double the time compared with that found in our patients with influenza (2.11 ± 0.5 hours).[21] The half-life of OC in the breast milk has not been previously reported. Taken together, our study provided the first maternal breast milk pharmacokinetic data for multiple-dose OP and its active metabolite OC in lactating patients with influenza.

Breastfed infants who are born to influenza-infected mothers are at a high risk of infection. Oseltamivir treatment of breastfeeding women might influence the treatment recommendations for their infants due to the potential exposure to the antiviral drug through breast milk. Thus, it is important to determine how oseltamivir concentration in the breast milk might influence dose recommendations for exclusively breastfed infants. The recommended dose of oseltamivir for 0 to 12-month-old infants is 3 mg/kg twice daily.[18] In our study, the calculated daily exposure to OP and OC (2.94 and 4.77 µg/kg/day, respectively) was < 0.1% of the recommended therapeutic dose. In the study by Greer *et al*., the infant exposure to OP was roughly estimated based on steady-state breast milk concentrations. This calculation resulted in 0.76 µg/kg/day approximated exposure of oseltamivir, which is lower than our estimations.[21] These differences are probably due to the used calculation methods and the different treatment protocols. Despite the differences between studies, our results indicate that the calculated oseltamivir exposure is negligible and significantly lower than the recommended therapeutic dosage for infants. Thus, from a benefit–risk perspective, the oral oseltamivir treatment of breastfeeding women should not affect the oseltamivir therapy of exclusively breastfed infants at risk of infection, and this clinical setting should not result in a different drug tolerability profile in such infants compared with influenza-infected infants treated with oseltamivir and breast fed from non-infected (and hence non-treated) women.

In conclusion, here, we provided the first maternal breast milk pharmacokinetic data for oral multiple-dose oseltamivir in breastfeeding patients with influenza. This is the first demonstration that the concentration of oseltamivir in the breast milk of patients with influenza is not sufficient to reach that of a therapeutic dose for breastfed infants, thus oral oseltamivir treatment of breastfeeding women does not influence the dosage recommendations for their infants who are at high risk for acquiring infection.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

P.F. is the founder and CEO and E.F., A.G., A.N., and P.B. are involved in the management of Pharmahungary Group, a group of R&D companies. S.T. was a paid consultant to F. Hoffmann–La Roche Ltd at the time of the study. M.A.K. is an employee and shareholder at Regeneron Pharmaceuticals, Inc. and was an employee of F. Hoffmann-La Roche Ltd. at the time of the study. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

E.F., R.N.N., M.A.K., P.V., A.G., and P.F. wrote the manuscript. E.F., S.T., P.V., and P.F. designed the research. E.F., A.N., P.B., and S.T. performed the research. M.A.K. and R.N.N. analyzed the data.

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