Oseltamivir and Oseltamivir Carboxylate Pharmacokinetics in Obese Adults: Dose Modification for Weight Is Not Necessary\textsuperscript{,†}

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Obesity is an independent risk factor for mortality in patients infected with pandemic influenza A virus (H1N1). Given the poor outcomes observed among adult obese patients with H1N1, the dosing of antiviral agents in this population has been questioned, and use of twice the standard oseltamivir dose has been suggested. However, studies evaluating the disposition of oseltamivir and oseltamivir carboxylate (the active metabolite) in the obese population are scant. We evaluated the single-dose and steady-state pharmacokinetics of oseltamivir (75 mg by mouth twice daily) in a cohort of 21 healthy adult volunteers with class III obesity (body mass index [BMI], \(\geq 40\) kg/m\(^2\)). The median (minimum, maximum) age, weight, and BMI were 36 (19, 50) years, 122 (106, 159) kg, and 43.7 (40.0, 54.4) kg/m\(^2\), respectively. The population pharmacokinetic exposure profiles of oseltamivir carboxylate (the active metabolite) were comparable between class III obese subjects and nonobese adults (healthy and infected). Similar to previous pharmacokinetic analyses in nonobese subjects, the mean (percent covariance [CV]) area under the concentration-time curve for the dosing interval (AUC\(_{0-50}\)) was 2,621 ng \(\cdot\) h/ml (17) for oseltamivir carboxylate. Body size was significantly \((P < 0.05)\) associated with oseltamivir and oseltamivir carboxylate apparent clearance, but the correlation coefficient was poor (\(R^2 \leq 0.3\)). Creatinine clearance estimated by the Cockcroft-Gault method and lean body weight were also significantly \((P < 0.05)\) but poorly \((R^2 = 0.17)\) correlated with oseltamivir and oseltamivir carboxylate apparent clearance. Since the systemic exposure of oseltamivir carboxylate is not reduced in class III obese adults with standard doses, a dose increment of oseltamivir is likely to be unnecessary.

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formed.

defining the concentration-time relationship between the parent and active me-

This descriptive analysis was performed to permit comparison of the pharmaco-

zero to 12 h, i.e., dosing interval (AUC 0–

After this last dose. Oseltamivir can be converted to oseltamivir carboxylate

were reviewed to verify adherence. Subjects returned to the clinical research unit

research unit. Six doses of oseltamivir were dispensed to subjects along with a

of water in the fasted state (no food 1 h prior and after dosing). The first dose

directly observed by the study personnel. Blood samples (2 ml each) were col-

20°C) as two aliquots (0.25 to 0.5 ml each) within 60 min of blood collection and at

oseltamivir carboxylate concentrations (4). To overcome this issue, all

plasma concentrations of oseltamivir and oseltamivir carboxylate (PRA method

were collected on wet ice in 2-ml vacutainer tubes that contained
glycolytic inhibitor, 3.0 mg sodium fluoride, and 6.0 mg disodium EDTA (4).

Plasma was harvested and stored frozen (−20°C) as two aliquots (0.25 to 0.5 ml
each) within 60 min of blood collection and at −70°C within 24 h of blood
collection until bioanalysis.

Sample bioassay. Plasma samples were analyzed by PRA International, Bio-
analytical Laboratory (Assen, Netherlands) using a previously validated liquid
chromatography-tandem mass spectrometry (LC-MS/MS) method to assay
plasma concentrations of oseltamivir and oseltamivir carboxylate (PRA method
1120). Deuterated oseltamivir (d3-Ro640796) and oseltamivir carboxylate (d3-
Ro640882) were utilized as the internal standards. The interassay coefficient of
variation of quality control samples was between 1.6% and 2.6% for oseltamivir
and 1.9% and 3.7% for oseltamivir carboxylate. The lower limits of quantitation
(LLOQ) for the parent compound and the active metabolite were 1 and 10 ng/ml,
respectively, in plasma.

Pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was
performed using Phoenix WinNonLin 6.1 program (Pharsight Corp., Mountain
View, CA). The following pharmacokinetic parameters were estimated: maxi-
mum concentration (Cmax), time to Cmax (Tmax), area under the curve from time
to 12 h, i.e., dosing interval (AUC0–12), and minimum concentration (Cmin).
This descriptive analysis was performed to permit comparison of the pharma-
cinetic data generated from the present study to those previously published (22).
However, given the limitations of noncompartmental analysis for appropri-
ately defining the concentration-time relationship between the parent and active me-
tabolite, a population pharmacokinetic (POP-PK) systems analysis was also per-
formed.
The relationships of body size to age, wt (kg), ht (cm), and BMI (kg/m²) were used through the population simulation option within ADAPT 5. The central tendency and distributions generated by our simulations were compared with those generated by our noncompartmental analysis and previous studies (14, 22). The scatter and median band profiles of the natural logarithm of transformed oseltamivir concentrations versus time after dose 9 are shown in Fig. 1A. The plasma pharmacokinetics estimates of oseltamivir are included in Table 2 by dose number (1 versus 9). Please note that Table 2 includes both the mean (SD) values and median (5th and 95th percentile) estimates to permit comparison of central tendency and data dispersion to previously published data. Of the 19 subjects studied at dose 9, one subject was suspected to have been noncompliant with the study protocol and data from this subject were excluded for dose 9. Specific details outlining the rationale for correlated with Vm/F, Clm/F, Vp/F, and CLm/F were incorporated into the POP-PK structural model. Assessment of the potential improvement in the POP-PK model fit was based on AIC. All statistical analyses in this study were performed using Stata SE version 11 (Stata Corp., College Station, TX). Non-linear regression of Vp/F, Clm/F, Vm/F, and CLm/F to body size and kidney function was evaluated using the dynamic curve-fitting option in SigmaPlot version 11 (Systat Software Inc., San Jose, CA).

### RESULTS

**Population demographics.** A total of 48 subjects were screened for participation in this study. The screened subjects included 40 females and 8 males with a median (minimum [min], maximum [max]) age of 40 (19, 54) years. Twenty-one subjects (17 female, 4 male) met the study criteria and were enrolled. The race/ethnicity of subjects were as follows: white (n = 11), black (n = 7), black and white (mixed-race, n = 1), and Hispanic (n = 2). A summary of the subject demographics is provided in Table 1. Twenty-one subjects completed the pharmacokinetic sampling after dose 1. Nineteen subjects completed the pharmacokinetic sampling after dose 9. One subject was withdrawn due to noncompliance with study procedures, which included missing more than one dose prior to the last scheduled pharmacokinetic sampling phase. The second subject withdrew voluntarily after reporting anxiety, lower back pain, pelvic spasms, breast pain, and shivers. These symptoms were evaluated as unrelated to the study medication by the study physician. No therapeutic interventions were required to address this potential adverse event.

**Oseltamivir noncompartmental pharmacokinetic analysis.** The scatter and median band profiles of the natural logarithm-transformed oseltamivir concentrations versus time after dose 9 are shown in Fig. 1A. The plasma pharmacokinetics estimates of oseltamivir are included in Table 2 by dose number (1 versus 9). Please note that Table 2 includes both the mean (SD) values and median (5th and 95th percentile) estimates to permit comparison of central tendency and data dispersion to previously published data. Of the 19 subjects studied at dose 9, one subject was suspected to have been noncompliant with the study protocol and data from this subject were excluded for dose 9. Specific details outlining the rationale for

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median value (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33 (19, 45)</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>146 (137, 159)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>46.3 (43.3, 54.4)</td>
</tr>
<tr>
<td>Ht (cm)</td>
<td>177 (168, 182)</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.92 (0.77, 0.99)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>132 (111, 166)</td>
</tr>
</tbody>
</table>

| (SD slope) was fit for the population but served as a fixed effect for individual patients. The initial estimates for the SD intercept were 0.0001 and 0.001 for the parent and metabolite, respectively, which equated to their LLOQ. The SD intercept was modified as necessary based on the fit of the model. Evaluation of the final POP-PK model was performed using diagnostic plots and the posterior predictive check methodology (23). The diagnostic plots included population and individual predicted-versus-observed plots, residuals versus time, and residuals versus individual predicted concentration. The goal of the posterior check evaluation approach was to confirm the agreement between model-based simulations and observed AUC<sub>0→t</sub>, C<sub>max</sub>, and C<sub>min</sub> estimates. To accomplish this goal, we simulated the concentration-time profile of oseltamivir carboxylate for 5,000 patients based on a regimen of 75 mg by mouth every 12 h for nine doses. The final mean POP-PK parameter and covariance matrix estimates were used through the population simulation option within ADAPT 5. The central tendency and distributions generated by our simulations were compared with those generated by our noncompartmental analysis and previous studies (14, 22).

### Correlation of pharmacokinetic parameters to body size and creatinine clearance.

The relationships of body size to V<sub>p/F</sub>, CL<sub>m/F</sub>, V<sub>m/F</sub>, and CL<sub>m/F</sub> were evaluated using linear and nonlinear regression-based methods. The body size descriptors that were evaluated included total body weight (TBW), ideal body weight (IBW), adjusted body weight (ABW), and lean body weight (LBW). The equations used to estimate these body size descriptors are provided below. The source and rationale for use of these equations has been described previously (12). TBW is the measured body weight, in kg. IBW (kg) for males = 50 + 0.906(height, in cm, over 152.4 cm); for women, IBW = 45.5 + 0.906(height, in cm, over 152.4 cm); ABW (in kg) = IBW + 0.4(TBW – IBW), LBW for males = (9,270 × TBW)/(6,680 × BMI); for females, LBW = (9,270 × TBW)/(8,780 + 244 × BMI).

Finally, the relationships of CL<sub>m/F</sub> and CL<sub>m/F</sub> to estimated creatinine clearance were evaluated by linear regression. Creatinine clearance was estimated using the Cockcroft-Gault equation and use of the above body size descriptors as the weight parameter (12). An additional assessment of the relationships between covariates and PK parameters, covariates identified to be significantly

### TABLE 2. Plasma oseltamivir and oseltamivir pharmacokinetic parameters after dose 1 and dose 9 in obese subjects receiving 75 mg of oseltamivir phosphate by mouth every 12 h in the fasted state

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter and statistic</th>
<th>Dose 1 (n = 21)</th>
<th>Dose 9 (n = 18)</th>
<th>Dose 1 (n = 21)</th>
<th>Dose 9 (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC&lt;sub&gt;0→t&lt;/sub&gt; (ng · h/ml)</strong></td>
<td>118 (72.1)</td>
<td>123 (62.4)</td>
<td>1,691 (411.8)</td>
<td>2,579 (510.3)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>97.5 (69.5, 402)</td>
<td>117 (64.7, 352)</td>
<td>1,702 (966.9, 2,517)</td>
<td>2,590 (1,866, 3,376)</td>
</tr>
<tr>
<td>Median (5th, 95th percentile)</td>
<td>59.7 (31.0)</td>
<td>59.4 (26.9)</td>
<td>223 (64.5)</td>
<td>316 (68.1)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>53.7 (18.0, 130)</td>
<td>51.1 (28.3, 122)</td>
<td>222 (111, 301)</td>
<td>301 (197, 433)</td>
</tr>
<tr>
<td>Median (5th, 95th percentile)</td>
<td>1.2 (0.49)</td>
<td>1.1 (0.86)</td>
<td>3.9 (1.3)</td>
<td>3.2 (0.79)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.0 (0.5, 2.0)</td>
<td>1.0 (0.5, 3.0)</td>
<td>3.5 (2.0, 6.0)</td>
<td>3.0 (1.5, 4.0)</td>
</tr>
<tr>
<td>Median (5th, 95th percentile)</td>
<td>2.1 (0.93)</td>
<td>1.6 (0.45)</td>
<td>41.2 (24.7)</td>
<td>113 (37.4)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.0 (1.1, 4.5)</td>
<td>1.5 (1.1, 2.6)</td>
<td>34.0 (13.8, 87.7)</td>
<td>109 (57.3, 193)</td>
</tr>
</tbody>
</table>

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exclusion of this subject are provided in the description of oseltamivir carboxylate pharmacokinetics below. The AUC\(_{0\rightarrow\tau}\) values were very similar between dose 1 and dose 9.

Oseltamivir carboxylate noncompartmental pharmacokinetic analysis. The scatter and median band profiles of the natural logarithm-transformed concentration-time profiles of oseltamivir carboxylate are shown in Fig. 1B after dose 9. The mean (SD) and median (and 5th and 95th percentile) plasma pharmacokinetic estimates of oseltamivir carboxylate are included in Table 2 by dose number (1 versus 9). Of note, the concentration-time profile of one subject was severalfold higher than that observed for other subjects within the group after dose 9, and this suggested that this subject was noncompliant with the study protocol. We suspect this patient self-administered 150 mg of oseltamivir phosphate a few hours prior to the scheduled ninth dose. This subject had an oseltamivir carboxylate concentration of 1,260 ng/ml; the geometric mean (90% confidence interval [CI]) value was 139 (119, 161) ng/ml prior to the ninth dose in the other subjects. The oseltamivir carboxylate concentration 12 h after administration of the ninth dose was 369 ng/ml in the one subject in comparison to a geometric mean (90% CI) of 113 (100, 129) ng/ml. A pre-ninth dose concentration (\(C_{\text{min-8}}\)) showed a 3.4-fold higher concentration than the concentration 12 h after the ninth dose (\(C_{\text{min-9}}\)). As a result, Table 2 excludes data from this subject for dose 9. The median AUC\(_{0\rightarrow\tau}\) and \(C_{\text{max}}\) values were 52% and 36% higher after dose 9 than dose 1. The \(T_{\text{max}}\) values were similar between dose 9 and dose 1. The median \(C_{\text{min}}\) value was approximately 3-fold higher after dose 9 than dose 1.

**Population pharmacokinetic analysis.** The initial four-compartment structural parent-to-metabolite model described in Materials and Methods and illustrated in Fig. 2 provided the most robust fit to the parent and metabolite concentration-time data. Models of increasing complexity (up to seven compartments) did not improve the goodness of fit and resulted in an increase in the AIC. Table 3 includes the population mean (and percent standard error [SE]) estimates for the eight pharmacokinetic parameters used to define the structural model. The population pharmacokinetic estimates for the parent were more variable than those of the metabolite. The residual standard errors were <15% for most of the parameter estimates, except for \(V_m/F\) (39.7%) and \(V_m/F\) (22.7%). Diagnostic plots of the population predicted versus observed concentrations suggested good population and individual predicted versus observed fits, with no clear bias for individual concentration prediction or time effect on the predicted concentration. The population model predicted-to-observed concentration fit is shown in Fig. 3 and was better for oseltamivir carboxylate \((R^2 = 0.92)\) compared to oseltamivir \((R^2 = 0.80)\). This difference in fit was expected based on the variability noted in the concentration-time profile of oseltamivir compared to oseltamivir carboxylate, as illustrated in Fig. 1. Despite this relative difference in model fit, use of the population model to simulate concentration-time profiles of 5,000 patients yielded comparable AUC\(_{0\rightarrow\tau}\), \(C_{\text{max}}\), and \(C_{\text{min}}\) values to those generated by our noncompartmental analysis approach (Table 4 and Table 2). The data distribution around the central tendency estimates were also comparable to previously published data and are described with more detail in the Discussion (14, 22).

As an additional post hoc model validation step, we modeled oseltamivir and oseltamivir carboxylate independently. We fit a three-compartment model with first-order absorption, elimination, and transfer for the parent and a two-compartment model with first-order absorption and elimination for the metabolite. The population pharmacokinetic estimates for the parent were more variable than those of the metabolite. The residual standard errors were <15% for most of the parameter estimates, except for \(V_m/F\) (39.7%) and \(V_m/F\) (22.7%). Diagnostic plots of the population predicted versus observed concentrations suggested good population and individual predicted versus observed fits, with no clear bias for individual concentration prediction or time effect on the predicted concentration. The population model predicted-to-observed concentration fit is shown in Fig. 3 and was better for oseltamivir carboxylate \((R^2 = 0.92)\) compared to oseltamivir \((R^2 = 0.80)\). This difference in fit was expected based on the variability noted in the concentration-time profile of oseltamivir compared to oseltamivir carboxylate, as illustrated in Fig. 1. Despite this relative difference in model fit, use of the population model to simulate concentration-time profiles of 5,000 patients yielded comparable AUC\(_{0\rightarrow\tau}\), \(C_{\text{max}}\), and \(C_{\text{min}}\) values to those generated by our noncompartmental analysis approach (Table 4 and Table 2). The data distribution around the central tendency estimates were also comparable to previously published data and are described with more detail in the Discussion (14, 22).

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**TABLE 3.** Pharmacokinetic parameters and interindividual variability estimates from the final population pharmacokinetic model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population mean</th>
<th>Interindividual variability (% CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>% SE</td>
</tr>
<tr>
<td></td>
<td>Interindividual</td>
<td>variability (% CV)</td>
</tr>
<tr>
<td></td>
<td>estimate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(K_e) (h(^{-1}))</td>
<td>1.20</td>
<td>14.9</td>
</tr>
<tr>
<td>(V_m/F) (liter)</td>
<td>775</td>
<td>39.7</td>
</tr>
<tr>
<td>(CL_{m2}/F) (liter/h)</td>
<td>35.1</td>
<td>12.4</td>
</tr>
<tr>
<td>(K_{23}) (h(^{-1}))</td>
<td>0.188</td>
<td>12.6</td>
</tr>
<tr>
<td>(K_{32}) (h(^{-1}))</td>
<td>0.0808</td>
<td>5.03</td>
</tr>
<tr>
<td>(K_{m1}) (h(^{-1}))</td>
<td>0.625</td>
<td>7.34</td>
</tr>
<tr>
<td>(V_{mF}/F) (liter)</td>
<td>17.7</td>
<td>22.7</td>
</tr>
<tr>
<td>(CL_{m1}/F) (liter/h)</td>
<td>27.6</td>
<td>2.09</td>
</tr>
</tbody>
</table>

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**FIG. 3.** Scatter and linear fit for the population predicted-versus-observed concentrations for oseltamivir (A) and oseltamivir carboxylate (B).
The population mean estimates were 743 liters ($V_p/F$), 45.2 liters/h (CL$_{p/F}$), 177 liters ($V_m/F$), and 28.5 liters/h (CL$_{m/F}$) for the parent (two-compartment) and metabolite (one-compartment) models that were constructed independently. As shown, the estimates derived by independent model assessments were similar to those generated by the parent-to-metabolite POP-PK comodel in Table 3.

**Correlation of pharmacokinetic parameters to body size and creatinine clearance.** When considering oseltamivir, linear regression of $V_p/F$ to body size descriptors yielded nonsignificant relationships with TBW ($P = 0.47$), IBW ($P = 0.77$), ABW ($P = 0.55$), and LBW ($P = 0.31$). Similarly, linear regression of CL$_{p/F}$ was not significantly related to TBW ($P = 0.063$). However, CL$_{m/F}$ was significantly but poorly correlated to IBW ($P = 0.035$; $R^2 = 0.21$), ABW ($P = 0.033$; $R^2 = 0.22$), and LBW ($P = 0.035$; $R^2 = 0.21$). For oseltamivir carboxylate, linear regression of $V_m/F$ also yielded nonsignificant relationships with TBW ($P = 0.42$), IBW ($P = 0.94$), ABW ($P = 0.63$), and LBW ($P = 0.61$). In contrast, a significant but also poor correlation was observed between CL$_{m/F}$ to all tested body size descriptors: TBW ($P = 0.013$; $R^2 = 0.25$), IBW ($P = 0.010$; $R^2 = 0.26$), ABW ($P = 0.006$; $R^2 = 0.30$), and LBW ($P = 0.010$; $R^2 = 0.27$). For pharmacokinetic parameters significantly correlated to body size, an $R^2$ value of $> 0.30$ was not observed with use of nonlinear (exponential rise to max, hyperbola models) curve-fitting options selected based on the scatter plot pattern.

The Cockcroft-Gault equation was used to estimate creatinine clearance, which was not significantly correlated to CL$_{m/F}$ with use of TBW ($P = 0.95$), IBW ($P = 0.70$), ABW ($P = 0.75$), or LBW ($P = 0.51$) as the weight parameter in this kidney function equation. Similarly, use of TBW ($P = 0.13$), IBW ($P = 0.086$), or ABW ($P = 0.069$) in the Cockcroft-Gault equation to estimate creatinine clearance did not have a significant correlation to CL$_{m/F}$. The exception to this analysis was noted with the use of LBW in the Cockcroft-Gault equation to estimate creatinine clearance. A significant ($P = 0.035$) but poor correlation ($R^2 = 0.17$) was observed between CL$_{m/F}$ and Cockcroft-Gault (with LBW) estimated creatinine clearance. Despite a significant relationship with CL$_{p/F}$, CL$_{m/F}$, and weight, incorporation of these body size descriptors as covariates into the POP-PK model resulted in an increase in the AIC. Similarly, inclusion of Cockcroft-Gault (with LBW) as a covariate of CL$_{m/F}$ also increased the AIC when tested in the POP-PK model. As a consequence, the final POP-PK model does not include these covariates.

**DISCUSSION**

Obesity has reached epidemic proportions in the United States and is now a global health problem (6, 20). One of every three Americans has class I obesity or higher, and 1 of every 20 Americans has class III obesity (6). Recent data have demonstrated adverse clinical outcomes among patients with obesity who were infected with the H1N1 pandemic strain (7, 10, 11, 18, 24). The higher rates of mortality in this obese population subset have raised concerns about the adequacy of the standard dose of oseltamivir phosphate as recommended in the current Tamiflu product label. These concerns prompted the current study.

Contrary to prevailing thinking, the collective results of our study indicate that oseltamivir dose adjustments are not required for individuals with obesity. We have focused our discussion on oseltamivir carboxylate, given that this compound is the pharmacologically active component, with comparative data widely available in the literature. Specifically, our findings are highly concordant with a recent comprehensive literature review by Widmer and colleagues regarding the pharmacokinetics and pharmacodynamics of oseltamivir carboxylate from over 20 clinical trials (22). In particular, a review of their comprehensive summary demonstrates with great clarity that the data from our study are well within the expected pharmacokinetic distributions of normal-weight subjects (22). In their evaluation of normal-weight healthy and infected subjects, the mean (SD) $C_{\text{max}}$ and $C_{\text{min}}$ values for oseltamivir carboxylate at 75 mg twice daily were 342 (83) ng/ml and 168 (32) ng/ml, respectively (22). In comparison, the $C_{\text{max}}$ and $C_{\text{min}}$ values in the current study were 316 (68.1) ng/ml and 113 (37.4) ng/ml. The AUC$_{0\rightarrow\infty}$ values were also markedly comparable; the AUC$_{0\rightarrow\infty}$ mean (SD) was 2,578 (510) ng · h/ml in our noncompartmental pharmacokinetic evaluation, compared to 3,220 (982) ng · h/ml reported by Widmer and colleagues. Our POP-PK model estimate of the mean (SD) AUC$_{0\rightarrow\infty}$ of 2,621 (441.0) ng · h/ml was also comparable. The Tamiflu product label (15) includes a mean (percent CV) AUC$_{0\rightarrow\infty}$ of 2,719 (20) ng · h/ml, which again was well in line with the estimates generated in the current study. These comparisons from multiple sources indicate that the exposure of oseltamivir carboxylate is not lower in obese compared to nonobese adults administered standard oseltamivir phosphate doses. Lastly, our findings are consistent with results generated through a POP-PK analysis of 115 nonobese male subjects by Rayner and colleagues (14). In that study of non-class III obese subjects, the population-simulated median (5th, 95th percentile) AUC$_{0\rightarrow\infty}$, $C_{\text{max}}$, and $C_{\text{min}}$ values for oseltamivir carboxylate were 12,098 (8,236, 18,207) ng · h/ml reported by Widmer and colleagues. Our

<table>
<thead>
<tr>
<th>Model statistic</th>
<th>Oseltamivir</th>
<th>Oseltamivir carboxylate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population estimate ($n = 5,000$)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC$_{0\rightarrow\infty}$ (ng · h/ml)</td>
<td>$C_{\text{max}}$ (ng/ml)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>157 (124)</td>
<td>44.0 (33.2)</td>
</tr>
<tr>
<td>Median</td>
<td>135</td>
<td>39.2</td>
</tr>
<tr>
<td>5th percentile</td>
<td>76.7</td>
<td>19.7</td>
</tr>
<tr>
<td>95th percentile</td>
<td>297</td>
<td>80.5</td>
</tr>
</tbody>
</table>

**TABLE 4. Simulated exposure estimates of oseltamivir and oseltamivir carboxylate following nine doses of oseltamivir phosphate**
ng·h/ml, 332 (231, 484) ng/ml, and 167 (101, 272) ng/ml, respectively, and again, these findings matched our results very closely. Several things should be noted when interpreting the results, especially considering the remarkable similarity in the pharmacokinetic profiles. First, our study included only noninfected, healthy obese subjects (17). We also did not study a normal-weight control group, which compromises direct comparisons and statistical inferences. This, however, does not minimize our findings. Ariano and colleagues recently demonstrated that the pharmacokinetics of oseltamivir carboxylate are not reduced in critically ill patients across a weight range of approximately 50 to 200 kg (2). The median (interquartile range [IQR]) AUC_{0-\infty} in critically ill patients with normal kidney function was 4,854 (3,109, 10,820) ng·h/ml (2), compared to a median (IQR) AUC_{0-\infty} of 4022 (3,481, 4,747) ng·h/ml in the current study (noncompartmental estimate). Similar to our findings, Ariano and colleagues also demonstrated that pharmacokinetic parameters of oseltamivir carboxylate are not influenced by body weight (2). Data from a previous single phase III trial also confirmed that the exposure of oseltamivir carboxylate is not altered secondary to infection (9).

An additional point to consider is the perception that plasma oseltamivir carboxylate concentrations do not reflect concentrations at the site of infection. Oseltamivir carboxylate is a small molecule (284.4 g/mol) that is virtually unbound to plasma proteins (3% protein binding) (4). Thus, lung exposures may be inferred from oseltamivir carboxylate plasma concentration-time data. Although we did not measure bronchoalveolar lavage fluid (BALF) drug concentrations to confirm this, lung penetration of this agent has been studied in the rat (5). The ratios of oseltamivir carboxylate BALF to plasma AUC_{0-\infty} and AUC_{0-\infty} have been demonstrated to be 1.05 and 1.51, respectively (5). These data are consistent with the expected tissue distribution of a low-molecular-weight and low-plasma protein-bound compound.

Finally, a phase II clinical trial evaluating the safety and efficacy of the standard dose (75 mg, twice daily) versus a high dose (150 mg, twice daily) of oseltamivir phosphate has been completed (NCT00298233). A second study evaluating the standard dose (75 mg, twice daily) versus a high dose (225 mg, twice daily) in critically ill patients with influenza is under way (NCT01010087). The results of these studies may alter our current oseltamivir dosing paradigm for critically ill patients with influenza. However, these studies are unlikely to suggest that higher doses are necessary secondary to obesity alone. The results of the current study as well as those outlined above will have a major impact on the CDC-SNS planning and procurement process. The CDC-SNS for oseltamivir may need to be increased if high-dose oseltamivir is demonstrated to be superior to standard doses among critically ill patients. However, our results indicate that this increase will not be driven by a need for higher doses in obese individuals to compensate for lower exposure profiles relative to nonobese individuals.

In summary, the current study of a cohort of young, healthy, obese class III subjects demonstrated that the plasma pharmacokinetics of oseltamivir and oseltamivir carboxylate are similar to those in nonobese class III subjects. These data verify that the apparent clearance of oseltamivir and oseltamivir carboxylate are poorly correlated to body weight in subjects over 100 kg. The current dose of oseltamivir phosphate indicated on the Tamiflu product label is expected to achieve comparable plasma oseltamivir and oseltamivir carboxylate exposures in adult subjects with class III obesity as those in nonobese subjects. Given that previous studies have determined that the POP-PK parameters of oseltamivir carboxylate are similar in healthy subjects and critically ill patients (2), the results of the current study are expected to be directly translatable to obese patients with influenza.

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