Prospective, Controlled Study of Acyclovir Pharmacokinetics in Obese Patients

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The current recommendations for intravenous (i.v.) acyclovir dosing in obese patients suggest using ideal body weight (IBW) rather than total body weight (TBW). To our knowledge, no pharmacokinetic analysis has validated this recommendation. This single-dose pharmacokinetic study was conducted in an inpatient oncology population. Enrollment was conducted by 1:1 matching of obese patients (>190% of IBW) to normal-weight patients (80 to 120% of IBW). All patients received a single dose of i.v. acyclovir, 5 mg/kg, infused over 60 min. Consistent with current recommendations, IBW was used for obese patients and TBW for normal-weight patients. Serial plasma concentrations were obtained and compared. Seven obese and seven normal-weight patients were enrolled, with mean body mass indexes of 45.0 and 22.5 kg/m², respectively. Systemic clearance was substantially higher in the obese than normal-weight patients (mean, 19.4 ± 5.3 versus 14.3 ± 5.4 liters/h; P = 0.047). Area under the concentration-time curve was lower in the obese patients (15.2 ± 2.9 versus 24.0 ± 9.4 mg·h/liter; P = 0.011), as was maximum concentration (5.8 ± 0.9 versus 8.2 ± 1.3 mg/liter; P = 0.031). Utilization of IBW for dose calculation of i.v. acyclovir in obese patients leads to lower systemic exposure than dosing by TBW in normal-weight patients. While not directly evaluated in this study, utilization of an adjusted body weight for dose determination appears to more closely approximate the exposure seen in normal-weight patients. (This study has been registered at ClinicalTrials.gov under registration no. NCT01714180.)

Thirty-five percent of adults older than 20 years of age are classified as obese (body mass index [BMI], ≥30 kg/m²) in the United States and an additional 34% as overweight (BMI, <30 but ≥25 kg/m²). Class III obesity (BMI, ≥40 kg/m²) has risen from 1.3% in the 1980s to 6.6% currently (1). Body composition is a major factor influencing drug pharmacokinetics (PK) and can alter several parameters, including volume of distribution (V) and clearance (CL) (2). Unfortunately, published PK data specific to obese patients are limited. While biomarkers and surrogate endpoints can direct dosing of certain agents, such as antihypertensives and lipid-lowering drugs, no such biomarkers exist for antivirals; thus, clinicians must rely on published PK and pharmacodynamic (PD) data.

Acyclovir is a nucleoside analogue that possesses activity against the herpes family of viruses, including herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) and varicella-zoster virus (VZV) (3). The efficacy of acyclovir for treating HSV has been linked to both area under the plasma concentration-time curve (AUC) and the time that drug concentration remains above the 50% inhibitory concentration (T > IC₅₀) (4–7). The T > IC₅₀ target that has been proposed is 50% of the dosing interval (4–9). Controversy exists regarding which of these PD parameters is most important in predicting clinical success.

The manufacturer recommends calculation of intravenous (i.v.) acyclovir dose to be based on total body weight (TBW); however, in obese patients it recommends dosing by ideal body weight (IBW) (3). The only literature to support this recommendation is a single PK analysis comparing morbidly obese (MO) to normal-weight (NW) healthy females, presented as an abstract in 1991 by Davis and colleagues (10). All participants received doses based on TBW. Dosing by TBW in MO patients resulted in approximately 2-fold-higher maximum concentrations than in NW patients. The authors concluded that dosing by TBW in MO patients was inappropriate and recommended the use of IBW in this population (10). The conclusions of this study remain to be validated. The decision to not use TBW in dosing morbidly obese patients is supported by at least one case of an obese patient developing acyclovir-induced renal failure following i.v. acyclovir dosed by TBW (11). A prospective evaluation of IBW to dose acyclovir in obese patients has not been published. The objective of the present study was to evaluate the PK of i.v. acyclovir in MO patients utilizing dosing recommendations from the manufacturer’s prescribing information.

(This study was presented in part at the 54th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, 2014.)

MATERIALS AND METHODS

Study design. This was a prospective, matched-pair study in patients admitted to an inpatient oncology ward. The primary outcome was difference in acyclovir systemic clearance (CL) between MO and NW patients. Secondary outcomes included AUC₀–τ, T > IC₅₀, using a standardized IC₅₀, and maximum concentration (Cmax). This study was approved by...
Acyclovir Pharmacokinetics in Obesity

Acyclovir pharmacokinetics. Pharmacokinetic parameter estimates for each patient’s data set were generated by the standard two-stage approach using compartmental modeling (WinNonlin version 2.1; Pharsight Corporation, Mountain View, CA) by the WVU Health Sciences Clinical Pharmacology Core. Selection of the most appropriate model for each patient’s data was primarily based on the Akaike information criterion. The absolute dose (nonnormalized) was utilized as the input variable for all analyses. Actual sample times obtained from initiation of the dose were calculated from the case report forms and used as primary input data. The optimal model was utilized to generate simulated data for estimation of the individual patients’ IC50 at steady state with 12-h dosing intervals. Evaluations of $T > IC_{50}$ were conducted using IC50 of 0.5625 mg/liter for HSV and 1.125 mg/liter for ZVZ, which had been reported previously and correspond to more resistant strains (8, 13).

Statistics. A sample size of 7 patients per group was estimated to provide an 80% power to detect a 19% difference in CL using a two-sided paired t test at significance level of 0.05 when the correlation coefficient is 0.15. In the data analysis of comparison on the primary and secondary outcomes, Wilcoxon signed-rank test was used for continuous variables with paired data and Wilcoxon rank sum test was used for continuous variables between two groups, while Fisher’s exact test was used in the data analysis between categorical variables. To explore optimal dosing strategies, CL was compared between MO and NW patients after normalizing by different measures of body size, including body surface area (BSA), TBW, IBW, lean body weight (LBW), and adjusted body weight (AJBW). AJBW was calculated as IBW plus 40% of TBW greater than IBW [AJBW = IBW + 0.4 × (TBW − IBW)] and LBW as previously described (14). Simple linear regression was performed to assess correlation of these body parameters with PK parameters. Analyses were considered statistically significant if $P$ was <0.05. All statistical analyses were performed using Stata (Stata statistical software, release 13, 2014; StataCorp LP, College Station, TX) and R software (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/).

RESULTS

A total of 14 patients were enrolled and completed the study (7 patients per group). Baseline data were similar between groups with the exception of TBW, BMI, percentage of IBW, and BSA (Table 1). All patients in the MO group were classified as class III obesity (BMI, ≥40 kg/m2). All patients were receiving acyclovir for prophylaxis with chemotherapy regimens with an anticipated prolonged duration of neutropenia. None of the patients in the study were febrile or neutropenic or had any signs of viral infection at the time of sampling.

CL was significantly higher in MO than NW patients, while AUCC0–2 and Cmax were significantly lower in MO patients (Table 2; Fig. 1). This difference in AUCC0–2 represents a 37% (95% con-

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**TABLE 1 Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Morbidly obese (n = 7)</th>
<th>Normal wt (n = 7)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.3 ± 9.6</td>
<td>53.0 ± 16.3</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Caucasian race (%)</td>
<td>7 (100.0)</td>
<td>7 (100.0)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>6 (85.7)</td>
<td>6 (85.7)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>120.5 ± 15.7</td>
<td>61.2 ± 5.1</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>57.1 ± 8.8</td>
<td>58.5 ± 5.5</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>% of IBW</td>
<td>212.4 ± 15.4</td>
<td>102.5 ± 10.7</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>45.0 ± 3.4</td>
<td>22.5 ± 2.2</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>2.3 ± 0.2</td>
<td>1.7 ± 0.1</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>SCr (mg/dl)</td>
<td>0.78 ± 0.26</td>
<td>0.76 ± 0.15</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²) (21)</td>
<td>93.4 ± 24.9</td>
<td>93.7 ± 25.7</td>
<td>0.94</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> BMI, body mass index; BSA, body surface area; GFR, glomerular filtration rate; IBW, ideal body weight; SCr, serum creatinine.

<sup>b</sup> Data are means ± standard deviations unless otherwise noted.

<sup>c</sup> Determined by the Wilcoxon rank sum or Fisher exact test, as appropriate.

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**TABLE 2 Comparison of mean pharmacokinetic parameters**

<table>
<thead>
<tr>
<th>Parameter&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Value for patients</th>
<th>Morbidly obese (n = 7)</th>
<th>Normal wt (n = 7)</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>285 ± 44</td>
<td>305 ± 26</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Cmax (mg/liter)</td>
<td>5.8 ± 0.9</td>
<td>8.2 ± 1.3</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td>AUCC0–2 (mg·hr/liter)</td>
<td>15.2 ± 2.9</td>
<td>24.0 ± 9.4</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Time &gt; 0.5625 mg/liter (min)</td>
<td>402.6 ± 204.2</td>
<td>524.3 ± 253.0</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Time &gt; 1.125 mg/liter (min)</td>
<td>264.9 ± 54.5</td>
<td>373.1 ± 181.6</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>CL (litters/h)</td>
<td>19.4 ± 5.3</td>
<td>14.3 ± 5.4</td>
<td>0.047</td>
<td></td>
</tr>
<tr>
<td>V (litters)</td>
<td>31.8 ± 9.9</td>
<td>25.9 ± 10.4</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> AUCC0–2, area under the curve from time zero to infinity; CL, systemic clearance; Cmax, maximum concentration; V, volume of distribution.

<sup>b</sup> Determined by the Wilcoxon signed-rank test.

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DISCUSSION

The objective of this study was to evaluate the currently recommended dosing strategy for i.v. acyclovir in MO patients. The PK parameters observed in the current study for NW patients are similar to those previously reported for healthy, nonobese patients. Average CL for NW patients in our study (14.6 liters/h/1.73 m²) was similar to that previously reported by Laskin and colleagues (16.1 liters/h/1.73 m²) (15, 16). Laskin and colleagues reported a similar AUC of 23.2 mg · h/liter in volunteer patients following a single dose of 5 mg/kg. While previous data (10, 11) have shown that using TBW for dose determination leads to excessive acyclovir exposure in obese patients, our study found that dosing by IBW will provide substantially lower exposure than in nonobese controls. Using patient-specific PK parameters in the MO patients, utilizing an AjBW to dose acyclovir would result in similar exposure (AUC∞) compared to our NW patients. While we agree with Davis and colleagues (10) that TBW leads to excess exposure in MO patients, dosing by AjBW (correction factor of 0.4) may more closely approximate drug exposure in NW patients. Utilizing BSA to dose obese patients may also result in exposure similar to that in NW patients; however, dosing by BSA is uncommon with antimicrobials and may lead to additional difficulties, as the dosing recommendation for i.v. acyclovir in NW patients is based on weight.

While the difference did not reach statistical significance, we found MO patients to have lower T>/IC₅₀ than NW patients (Table 2). With dosing every 12 h, a similar number of MO and NW patients achieved the T>/IC₅₀ goal of 50% in plasma for both HSV (57.1% and 71.4% for MO and NW patients; P = 1.0) and VZV (14.3% and 42.9% for MO and NW patients; P = 0.56). Note that achievement of this target is based on samples collected from blood and is likely different from PD parameters in other body compartments.

Limited studies evaluating dosing of acyclovir and valacyclovir for treatment of genital herpes suggest that AUC and T>/IC₅₀ are both associated with efficacy (4–7). It should be noted that genital herpes is commonly treated with oral rather than i.v. acyclovir. Unfortunately, trials evaluating the PD of i.v. acyclovir in treating
more invasive infections, such as HSV encephalitis, are lacking, and extrapolation of PD targets may not be appropriate.

Several important limitations exist in this study. First, our study was conducted with lower doses of i.v. acyclovir (5 mg/kg). While escalating doses result in linear increases in AUC and similar V (15, 17), caution should be exercised in extrapolating these data to other dosing regimens. Second, these patients were all receiving acyclovir for prophylaxis and were not actively infected or critically ill. Altered PK are often present in patients that are critically ill (18, 19). Third, our study evaluated the PK from blood samples only. Concentrations at different body sites, such as in cerebral spinal fluid, were not evaluated in this study and the PK parameters obtained in our study cannot be easily transposed to these body sites. Fourth, we evaluated only obese patients with BMIs of $\geq 40$ kg/m$^2$ (class III obesity) and did not include any patients with BMIs from 25.0 to 39.9 kg/m$^2$. Finally, these were cancer patients receiving active chemotherapy treatments, but we have no reason to believe this would affect the PK characteristics with i.v. administration compared to nononcology patients.

**Conclusions.** Our data suggest that MO (BMI, $\geq 40$ kg/m$^2$) patients treated with i.v. acyclovir dosed by IBW experience substantially decreased overall exposure compared to NW patients dosed by TBW. While not directly evaluated in this study, utilization of an AjBW (IBW + 0.4 × (TBW − IBW)) appears to more closely approximate the exposure seen in NW patients. Future research is needed to verify this finding and to explore appropriate dosing in this population and in other classes of obesity.

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