Steady-State Pharmacokinetics of Lamivudine in Human Immunodeficiency Virus-Infected Patients with End-Stage Renal Disease Receiving Chronic Dialysis

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The steady-state pharmacokinetics of lamivudine were evaluated in 11 subjects with human immunodeficiency virus infection and end-stage renal disease, 9 of whom were receiving hemodialysis and 2 of whom were receiving chronic ambulatory peritoneal dialysis (CAPD). All subjects received 150 mg of lamivudine daily for at least 2 weeks prior to sampling for determination of the pharmacokinetics of lamivudine over a 24-h period on 2 consecutive days. On the first day, subjects received 150 mg of oral lamivudine and underwent dialysis (hemodialysis or CAPD). On the second day, subjects received another 150 mg of oral lamivudine but dialysis was not performed. For the subjects undergoing hemodialysis, the geometric mean predose serum lamivudine concentration was 1.14 μg/ml (95% confidence interval [CI], 0.83 to 1.58 μg/ml), the geometric mean maximum concentration in serum (Cmax) was 3.77 μg/ml (95% CI, 3.01 to 4.71 μg/ml), and the geometric mean area under the serum concentration-time curve from time zero to 24 h (AUC0-24) was 49.8 μg·h/ml (95% CI 39.1 to 63.6 μg·h/ml). Hemodialysis removed approximately 28 mg of lamivudine but had no significant effect on Cmax or AUC0-24. In the absence of hemodialysis, the geometric mean lamivudine terminal elimination half-life was 17.2 h (95% CI, 10.5 to 28.1 h), whereas the geometric mean intradialysis half-life of lamivudine was 5.3 h (95% CI, 3.4 to 8.2 h). The pharmacokinetics of lamivudine in subjects undergoing CAPD were similar to those in subjects undergoing hemodialysis. CAPD removed 24 mg of lamivudine over a 24-h period but had no effect on Cmax or AUC0-24. Pharmacokinetic modeling suggests that a lamivudine dose of 25 mg daily in hemodialysis subjects would provide serum exposure similar to that provided by a dose of 150 mg twice daily in patients with normal renal function.

Renal insufficiency in human immunodeficiency virus (HIV) type 1 (HIV-1)-infected patients is becoming more common (18). This is due in part to the development of an HIV-associated nephropathy (HIVAN), characterized by massive proteinuria and rapidly progressive renal failure, in a subset of patients infected with HIV (8, 13, 24). Although combination antiretroviral therapy appears to slow the progression of HIVAN to end-stage renal disease (ESRD) in many cases (9, 16, 27), the total number of persons with ESRD due to HIVAN is expected to increase due to the increasing prevalence of HIV-1 infection (E. J. Schwartz, L. Szczeczeń, J. A. Winston, and P. E. Klotman, J. Am. Soc. Nephrol. 11:abstr. A0882, 2000). In addition to HIVAN, conditions such as hypertension, diabetes, or other glomerular diseases including membranoproliferative glomerulonephritis, amyloidosis, acute immune complex glomerulonephritis, cryoglobulinemia, and immunoglobulin A nephropathy may lead to ESRD in HIV-infected patients (1, 4, 10, 14, 15, 19, 22–25). HIV infection has become the third most frequent cause of renal failure among African Americans ages 20 to 64 (18). As HIV-infected patients continue to live longer and as the number of HIV-infected patients with ESRD continues to increase, the importance of understanding the pharmacokinetic properties of antiretroviral drugs in patients with ESRD becomes more crucial.

Lamivudine (Epivir; GlaxoSmithKline) is an antiretroviral drug commonly used to treat HIV infection. It is a cytosine dideoxynucleotide analogue prodrug that is phosphorylated within cells to an active triphosphate form which acts as a potent inhibitor of HIV reverse transcriptase. Although active as monotherapy against HIV, lamivudine should always be used in combination with other antiretroviral agents in order to achieve more effective suppression of viral replication and prevent the development of resistance (3, 5, 20, 21, 26). Antiretroviral combinations that include lamivudine decrease HIV viral loads to low or undetectable levels in a majority of patients (5) and delay the development of AIDS-defining events or death (6). Because it is primarily excreted in the urine, an understanding of the pharmacokinetic properties of lamivudine in patients with ESRD is important to guide dosing recommendations.

The pharmacokinetics of a single 300-mg dose of lamivudine...
were previously studied in HIV-infected subjects with normal renal function, moderate renal impairment, or severe renal impairment (7). In comparison to subjects with normal renal function, those with impaired renal function had higher peak concentrations in serum, longer terminal elimination half-lives ($t_{1/2\alpha}$), and larger areas under the serum concentration-time curves (AUCs). On the basis of the results of that study, the recommended dosage of lamivudine in patients with severe renal impairment is 25 mg once daily rather than the standard dose of 150 mg twice daily. However, the study did not evaluate the effect of dialysis on the pharmacokinetics of lamivudine. The low molecular weight, low level of protein binding, high degree of water solubility, and high degree of permeability exhibited by lamivudine suggest that it would be readily removed by dialysis (11, 12). A single-dose pharmacokinetic study of lamivudine in HIV-negative subjects undergoing hemodialysis indicated that although hemodialysis removed up to 50% of dialyzed lamivudine, it did not reduce the concentrations in serum to a clinically significant extent because of a large apparent volume of distribution (12). Neither of these single-dose studies assessed the pharmacokinetics of lamivudine at steady state.

The present study was designed to evaluate the pharmacokinetics of lamivudine at steady state in a cohort of HIV-infected subjects with ESRD receiving combination antiretroviral therapy that included lamivudine. All subjects were also undergoing chronic hemodialysis or chronic ambulatory peritoneal dialysis (CAPD).

**MATERIALS AND METHODS**

**Patient population.** HIV-infected subjects with ESRD requiring dialysis (hemodialysis or CAPD) were recruited. Subjects were included in the study if they were men or nonpregnant nonlactating women ages 18 or older, had evidence of HIV-1 infection confirmed by a positive antibody test result, were receiving combination antiretroviral therapy that included lamivudine, and had no significant hematologic, hepatic, or pancreatic dysfunction. Subjects were not eligible to participate in the study if they had medical conditions that could compromise their safety or interfere with the pharmacokinetic measurements, were active substance abusers, or had a history of sensitivity to lamivudine. Nine subjects undergoing hemodialysis and two subjects undergoing CAPD were studied.

**Study design.** This open-label, single-center study was approved by the Duke University Investigational Review Board, and all subjects gave written, informed consent before any study procedures were performed. All study participants had been receiving lamivudine for at least 3 months prior to enrollment in the study. At the time of enrollment, the lamivudine dosage was standardized to 150 mg orally once daily as part of combination antiretroviral therapy and was continued for at least 14 days with maintenance of the subject’s usual dialysis schedule and other medications. For subjects receiving hemodialysis, lamivudine was taken shortly after the completion of dialysis on dialysis days. Subjects receiving hemodialysis and CAPD were dialyzed three times per week; subjects receiving CAPD exchanged dialysate four times daily. After this 14-day lead-in period, subjects were admitted to the Duke Clinical Research Unit for sampling for pharmacokinetic studies.

For subjects receiving hemodialysis, a predose serum sample was obtained on hospital day 1. After oral administration of 150 mg of lamivudine, serum samples were obtained at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 20 h. Approximately 20 h after administration of the lamivudine dose hemodialysis was then performed over 3.5 to 4 h with GFS-20 dialysis membranes. A predialysis serum sample was obtained 24 h after dosing with dose 1 and a second 150-mg dose of lamivudine was administered. Serum samples were again obtained at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h postdosing.

For subjects undergoing CAPD, a predose serum sample was drawn on the morning of hospital day 1, a peritoneal dialysis exchange was completed, and a 150-mg dose of lamivudine was administered. Serum samples of lamivudine were then obtained at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h postdosing. During this period, subjects continued their usual CAPD schedule. Immediately prior to each exchange, a sample of the peritoneal dialysate was collected. On hospital day 2, a predose serum sample was again drawn (corresponding to a sample obtained 24 h after dosing with dose 1) and a second 150-mg dose of lamivudine was administered. CAPD was withheld and serum samples were obtained by using the same sampling schedule described above, the next 24 h postdosing, for a total of 70°C and transferred on dry ice to Glaxo Wellcome, Inc., for analysis. Lamivudine concentrations in serum and peritoneal dialysate fluid were determined by a validated high-performance liquid chromatography (HPLC) assay, followed by tandem mass spectrometry by the multiple reaction monitoring (MRM) technique.

For serum samples, lamivudine and its stable isotope-labeled internal standard were extracted from dialysate solution by using Waters Oasis HLB 30-mg solid-phase extraction plates. The eluent was analyzed by HPLC with a reverse-phase column and detection by tandem mass spectrometry by the positive-ion MRM technique. The calibration range for this method is 2.5 to 5,000 ng/ml with a 0.10-ml dialysate solution. The concentrations of lamivudine in samples were determined by interpolation from calibration curves based on linear regressions of the ratios of the peak area for the lamivudine calibration standard to the peak area for the isotopically labeled standard versus the corresponding nominal lamivudine concentrations by using a weighting factor of 1/concentration². The interassay precision of the assay, expressed as the coefficient of variation, was less than 12.1%. The accuracy of the assay, expressed as percent bias, was less than 4.9%.

For dialysate samples, lamivudine and its stable isotope-labeled internal standard were extracted from dialysate solution by using Waters Oasis HLB 30-mg solid-phase extraction plates. The eluent was analyzed by HPLC with a reverse-phase column and detection by tandem mass spectrometry by the positive-ion MRM technique. The calibration range for this method is 2.5 to 600 ng/ml with a 0.10-ml dialysate solution. The concentrations of lamivudine in dialysate samples were determined by interpolation from calibration curves based on linear regressions of ratios of the peak area for the lamivudine calibration standard to the peak area for the internal standard versus the corresponding nominal lamivudine concentrations by using a weighting factor of 1/concentration². The interassay precision of the assay, expressed as the coefficient of variation, was less than 9.1%. The accuracy of the assay, expressed as percent bias for validation control samples, was less than 12.4%.

**Pharmacokinetic analysis.** Noncompartmental methods were used to determine the values of the pharmacokinetic parameters for lamivudine, including the AUC from time zero to 24 h (AUC0-24) and $t_{1/2\alpha}$. The maximum concentration in serum ($C_{max}$), the predose concentration in serum ($C_{0}$), and the concentration in serum at 24 h postdosing ($C_{24}$) were obtained by direct inspection of the time concentration vs. time plots. These parameters were used for the calculation of the amount of lamivudine given. The results are presented as geometric means and 95% confidence intervals (CIs) for each parameter. Pharmacokinetic modeling was performed with WinNonlin software (version 2.1; Pharsight Corporation) to explore the feasibility of using different dosing regimens and schedules in our cohort undergoing hemodialysis. Data from the hemodialysis day were simulated by use of a one-compartment model with first-order absorption and elimination with an absorption lag (WinNonlin). $t_{max}$, the time to $C_{max}$, and AUC over the dosing interval were calculated for multiple dosing regimens, including 25 mg daily, 50 mg daily, 50 mg every other day, 75 mg every other day, and 150 mg weekly.

Simultaneous arterial and venous blood samples obtained during hemodialysis were used to calculate an extraction ratio, defined as $(C_{a} - C_{v})/C_{a}$, where $C_{a}$ is the concentration of lamivudine in arterial serum and $C_{v}$ is the concentration of lamivudine in venous serum. In addition, clearance of lamivudine by hemodialysis was calculated by the equation $Q_H \left[1 - (H + K_H) \cdot (C_{a} - C_{v})/C_{a}\right]$, where $Q_H$ is the blood flow rate through the dialysis filter, $H$ is the hematocrit, $K$ is the concentration of lamivudine in red blood cells/concentration of lamivudine in plasma reported previously (12), and $C_{a}$ and $C_{v}$ are as defined above. Since in vitro studies indicate that lamivudine partitions equally between red blood cells and plasma (12), a value of 1 was used for $K$. The amount of lamivudine removed during hemodialysis was estimated by dividing [lamivudine]·ER·F·T, where [lamivudine] is the mean arterial lamivudine concentration during the dialysis session, ER is the extraction ratio, F is the blood flow rate, and $T$ is the duration of dialysis. The amount of lamivudine removed by CAPD was determined by multiplying the concentration of lamivudine in the dialysate at the end of each dialysis dwell by the dialysate volume.
Results

Nine subjects receiving hemodialysis and two subjects receiving CAPD successfully completed the study with no treatment-related adverse events. All study subjects were male, 10 were African American, and 1 was Caucasian. Subjects had a median age of 49 years (range, 38 to 56 years), a median weight of 67 kg (range, 56 to 88 kg), a median CD4+ absolute T-cell count of 338 cells/mm$^3$ (range, 51 to 634 cells/mm$^3$), and a median CD4+ percentage of 19% (range, 7 to 35%). More than half of the subjects had HIV RNA levels below the lower limit of detection; thus, the median was below the lower limit of detection of <400 copies/ml. The range of HIV RNA levels was <50 to 71,770 copies/ml. Subjects had been diagnosed with HIV infection for a median of 5 years (range, 1 to 11 years), had been dialyzed for a median of 19 months (range, 3 to 71 months), and had been receiving lamivudine therapy for a median of 22 months (range, 5 to 48 months). The usual lamivudine dosing regimen prior to participation in the study was 150 mg orally once daily in seven subjects, 150 mg orally three times a week after dialysis in three subjects, and 150 mg orally twice daily in one subject.

Nondialysis day. Steady-state pharmacokinetics were similar on the nondialysis day for subjects undergoing hemodialysis and subjects undergoing CAPD and are depicted in Tables 1 and 2, respectively. In the cohort undergoing hemodialysis, the observed geometric mean $C_{\text{max}}$ was 3.24 μg/ml (95% CI, 2.61 to 4.02 μg/ml) and the observed geometric mean AUC$_0$–$C_{\text{max}24}$ was 46.5 μg·h/ml (95% CI, 37 to 58.4 μg·h/ml). Serum lamivudine concentrations before dosing and at 24 h postdosing were similar: 0.81 μg/ml (95% CI, 0.59 to 1.1 μg/ml) and 1.28 μg/ml (95% CI, 0.96 to 1.71 μg/ml), respectively. The apparent $t_{1/2}$ was 17.2 h (95% CI, 10.5 to 28.1 h). Among the cohort undergoing CAPD, the observed geometric mean $C_{\text{max}}$ was 4.5 μg/ml and the observed geometric mean AUC$_0$–$C_{24}$ was 65.7 μg·h/ml. Serum lamivudine concentrations before dosing and at 24 h postdosing were similar: 1.77 and 1.88 μg/ml, respectively. The apparent $t_{1/2}$ among these subjects was 20 h.

Dialysis day. Pharmacokinetic parameters observed under the influence of dialysis were similar to those observed on a nondialysis day both for subjects undergoing hemodialysis and for subjects undergoing CAPD (Tables 1 and 2), except that the apparent intradialysis $t_{1/2}$ among subjects undergoing hemodialysis was reduced to 5.3 h (Table 1). A graphical representation of the mean serum lamivudine concentration-versus-time profile for the hemodialysis cohort is shown in Fig. 1A. Comparison of simultaneous concentrations in arterial and venous blood during the hemodialysis session demonstrated that the lamivudine extraction ratios remained fairly constant throughout the session, with a mean extraction ratio of 0.318, verifying the removal of lamivudine during hemodialysis. The geometric mean clearance of lamivudine during hemodialysis among the nine study subjects was calculated to be 138 ml/min (range, 61 to 191 ml/min), and the amount of lamivudine removed during the dialysis session was estimated to be approximately 28 mg. Interestingly, mean serum lamivudine levels rose rapidly immediately after the hemodialysis session, with a mean postdialysis $C_{\text{max}}$ of 1.77 and 1.88 μg/ml, respectively. The apparent $t_{1/2}$ for serum lamivudine by dialysis was not of sufficient magnitude to cause a statistically significant change in $C_{\text{max}}$ or AUC$_0$–$C_{24}$.

Pharmacokinetic modeling of our data indicated that a lamivudine dose of 25 mg once daily among HIV-infected patients undergoing hemodialysis would provide concentrations in serum approximating those seen in patients with normal renal function receiving 150 mg twice daily (Fig. 2). In our subject with the lowest AUC for the 24-h dosing interval, a postdialysis dose of 25 mg daily would yield an AUC of 4.42 μg·h/ml, with a $C_{\text{max}}$ of 206 ng/ml and a $C_0$ of 100 ng/ml.

Among the subjects undergoing CAPD the amount of lamivudine removed by peritoneal dialysis was calculated by measuring the amount of lamivudine in the dialysate. The total measured amount of lamivudine removed in the peritoneal dialysate over a 24-h period was 23.5 mg in one subject and 24.8 mg in the other. For these subjects, pharmacokinetic profiles for lamivudine were obtained in the

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**TABLE 1. Lamivudine pharmacokinetic parameters for the nine subjects undergoing hemodialysis**

<table>
<thead>
<tr>
<th>Dose</th>
<th>$C_0$ (μg/ml)</th>
<th>$C_{\text{max}}$ (μg/ml)</th>
<th>$C_{24}$ (μg/ml)</th>
<th>AUC$<em>0$–$C</em>{24}$ (μg·h/ml)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean</td>
<td>95% CI</td>
<td>Geometric mean</td>
<td>95% CI</td>
<td>Geometric mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>1</td>
<td>1.14</td>
<td>0.83–1.58</td>
<td>3.77</td>
<td>3.01–14.71</td>
<td>0.81</td>
</tr>
<tr>
<td>2</td>
<td>0.81</td>
<td>0.59–1.1</td>
<td>3.24</td>
<td>2.6–4.02</td>
<td>1.28</td>
</tr>
</tbody>
</table>

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**TABLE 2. Lamivudine pharmacokinetic parameters for two subjects receiving CAPD**

<table>
<thead>
<tr>
<th>Subject no. and dose</th>
<th>$C_0$ (μg/ml)</th>
<th>$C_{\text{max}}$ (μg/ml)</th>
<th>$C_{24}$ (μg/ml)</th>
<th>AUC$<em>0$–$C</em>{24}$ (μg·h/ml)</th>
<th>$t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.41</td>
<td>4.40</td>
<td>1.40</td>
<td>57.6</td>
<td>19.7</td>
</tr>
<tr>
<td>2</td>
<td>1.40</td>
<td>4.62</td>
<td>1.57</td>
<td>56.1</td>
<td>13.8</td>
</tr>
<tr>
<td>Subject 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2.35</td>
<td>4.88</td>
<td>2.25</td>
<td>73.9</td>
<td>25.6</td>
</tr>
<tr>
<td>2</td>
<td>2.25</td>
<td>4.40</td>
<td>2.26</td>
<td>77.0</td>
<td>29.1</td>
</tr>
</tbody>
</table>

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*a* Dose 1 was administered with CAPD, and dose 2 was administered without CAPD.
presence of CAPD (dose 1) or the absence of CAPD (dose 2) (Table 2). Figure 1B shows a graphical representation of the mean concentration-time profile for these two subjects. Although CAPD removed approximately 16% of the daily oral dose of lamivudine, withholding CAPD for 1 day did not significantly alter the pharmacokinetic parameters.

**DISCUSSION**

The purpose of this study was to evaluate the steady-state pharmacokinetics of lamivudine in HIV-infected patients with ESRD in order to determine the appropriate dose for such subjects. We believed that it was important to perform...
AUC0-12 was 4.57 to 6.63. Lamivudine at a dose of 150 mg orally every 12 h, the
In HIV-infected patients with normal renal function taking
that this dose is considerably higher than the dose needed.
hemodialysis. The data from this study suggest, however,
commonly been used for patients with ESRD undergoing
impairment (12). In clinical practice, a dose of 150 mg of
metabolism contributes little to the overall metabolism of the drug, this
pathway becomes more important in patients with renal
impaired (12). In clinical practice, a dose of 150 mg of
lamivudine given orally once daily is well tolerated and has
commonly been used for patients with ESRD undergoing
hemodialysis. The data from this study suggest, however,
that this dose is considerably higher than the dose needed.
In HIV-infected patients with normal renal function taking
lamivudine at a dose of 150 mg orally every 12 h, the
AUC0-12 was 4.57 to 6.63 μg·h/ml (2), whereas the AUC
over a 24-h dosing interval was 49.8 μg·h/ml in our hemo-
dialysis subjects taking 150 mg of lamivudine orally once
daily. Pharmacokinetic modeling of data for the subject with
the lowest AUC in our hemodialysis cohort indicated that
administration of a dose of 25 mg once daily would yield an
AUC over the dosing interval approximating that for sub-
jects with normal renal function receiving 150 mg twice
daily. Because of the prolonged $t_{1/2}$ of lamivudine in patients

![Graph showing lamivudine concentration-time profiles](http://aac.asm.org/)

**FIG. 2.** Lamivudine concentration-time profiles for observed and modeled data for subjects with ESRD and for subjects with normal renal function (2). The serum lamivudine concentrations in subjects with ESRD undergoing hemodialysis in the present study, who received 150 mg every 24 h, are compared with the serum lamivudine concentrations in subjects with normal renal function receiving 150 mg of lamivudine every 12 h (2). Also depicted here are results of phar-
camokinetic modeling for our subject with the lowest serum lamivudine concentrations and projections of the serum concentration-ver-
sus-time curves for lamivudine dosed at 25 mg every 24 h (qd) and 75 mg every 48 h (qod). HD, hemodialysis; bid, twice a day.

our evaluations at steady state because single-dose studies may fail to recognize the contributions of the drug distribution
in tissue or alternative routes of metabolism or elimination induced by prolonged exposure to a drug. For example,
in addition to renal elimination, lamivudine is also metabolized through a hepatic pathway (12). Although in patients
with normal renal function hepatic metabolism contributes little to the overall metabolism of the drug, this
pathway becomes more important in patients with renal
impairment (12). In clinical practice, a dose of 150 mg of
lamivudine given orally once daily is well tolerated and has
commonly been used for patients with ESRD undergoing
hemodialysis. The data from this study suggest, however,
that this dose is considerably higher than the dose needed.
In HIV-infected patients with normal renal function taking
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AUC0-12 was 4.57 to 6.63 μg·h/ml (2), whereas the AUC
over a 24-h dosing interval was 49.8 μg·h/ml in our hemo-
dialysis subjects taking 150 mg of lamivudine orally once
daily. Pharmacokinetic modeling of data for the subject with
the lowest AUC in our hemodialysis cohort indicated that
administration of a dose of 25 mg once daily would yield an
AUC over the dosing interval approximating that for sub-
jects with normal renal function receiving 150 mg twice
daily. Because of the prolonged $t_{1/2}$ of lamivudine in patients
with ESRD, an alternative dosing regimen of 75 mg every
other day would be expected to provide similar levels (Fig.
2). For hemodialysis patients for whom adherence to med-
ication regimens is an issue, this could potentially provide a postdialysis dosing schedule that would allow directly ob-
served therapy. This would be most helpful if other antiret-
roviral agents could be administered in a similar fashion.

These alternative lamivudine dosing regimens used in the
present study (25 mg daily or 75 mg every other day) were
suggested on the basis of pharmacokinetic data derived from
measurements obtained with serum. Potentially, serum lami-
vudine levels do not accurately reflect the level of the active
triphosphate form of lamivudine at the site of action in HIV-
infected cells. Since lamivudine triphosphate concentrations in
peripheral blood mononuclear cells have been measured and
 correlated with the concentrations in serum, reasonable infer-
ences regarding intracellular concentrations in our cohort can
be made (17). Recognizing, however, the dangers inherent in
underdosing and the excellent tolerability of the higher lami-
vudine doses used in this study, the common practice of dosing
patients with ESRD with doses higher than 25 mg remains a
reasonable option.

Although our study was not designed to evaluate differences
between hemodialysis and CAPD on the pharmacokinetics of
lamivudine, our results indicate that the amount of lamivudine
removed by dialysis and the values of the pharmacokinetic
parameters such as AUC0-24 were similar in both groups. He-
modialysis removed approximately 28 mg of lamivudine during
a standard 3.5-h session. This was sufficient to change the
apparent lamivudine $t_{1/2}$ from approximately 16 h in the ab-
sence of hemodialysis to 5.2 h during the dialysis session.
Immediately after hemodialysis, the serum lamivudine level in-
creased, probably due to redistribution from the intracellular
compartment. One implication of this finding is that hemodi-
alysis may not be effective in eliminating lamivudine from the
body in the setting of a lamivudine overdose. Our data also
demonstrated that a measurable amount of lamivudine, 16% of
the daily dose administered, was eliminated from the body
in the peritoneal dialysate in the patients undergoing CAPD. Although both hemodialysis and CAPD removed lamivudine,
the magnitude of the elimination by either route was insuf-
icient to meaningfully alter the measured AUC0-24 of the drug.
This suggests that the amount of lamivudine removed by dial-
ysis (CAPD or hemodialysis) is small relative to the total body
pool of lamivudine.

Finally, none of our study participants experienced adverse
events related to lamivudine therapy, even though many of
these patients had been taking lamivudine at a dose of 150 mg
daily for many months and had AUC0-24 five times those for
patients with normal renal function. This suggests that lami-
vudine is a relatively safe drug with a high therapeutic index.
Given the increasing prevalence of HIV-infected patients with
ESRD, understanding the pharmacokinetics of lamivudine is
important to enable clinicians to treat their patients safely and
effectively.

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REFERENCES


