Pharmacokinetics of Linezolid in Subjects with Renal Dysfunction

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Linezolid is a member of a new, unique class of synthetic antibacterial agents called oxazolidinones that are effective against gram-positive bacteria, including vancomycin-resistant organisms. We tested the hypothesis that the linezolid clearance would not be altered in subjects with renal dysfunction. Twenty-four subjects with renal function that ranged from normal to severe chronic impairment were enrolled, including patients with end-stage renal disease who were maintained on hemodialysis. Hemodialysis subjects were studied while they were on and off dialysis. Linezolid was administered as a single oral 600-mg dose, and plasma and urine samples were assayed for linezolid and metabolites for 48 h for all subjects and for up to 96 h for those subjects with impaired renal function not on dialysis. The total apparent oral clearance of linezolid did not change with renal function and ranged from 92.5 to 109.6 ml/min for subjects not requiring dialysis. For subjects on dialysis, the total apparent oral clearance increased from 76.6 ml/min on their off-dialysis day to 130.0 ml/min on their on-dialysis day. Approximately one-third of the dose was removed by dialysis. However, those subjects with severe renal insufficiency (creatinine clearance, <40 ml/min) and those with end-stage renal disease maintained on hemodialysis had higher concentrations of both metabolites. We conclude that no adjustment of the linezolid dosage is needed in subjects with renal dysfunction or subjects on hemodialysis.

Linezolid is a member of a new, unique class of synthetic antibacterial agents called oxazolidinones effective against many gram-positive bacteria, including vancomycin-resistant organisms. Linezolid selectively inhibits bacterial protein synthesis by binding to bacterial 23S rRNA of the 50S subunit and prevents the formation of a functional 70S initiation complex. Although the mode of action has not yet been fully determined, it is likely that oxazolidinones interfere with early steps in protein synthesis (7). The components of protein synthesis targeted by this group of compounds do not appear to be recognized by other antibacterial agents since no cross-resistance has been found in strains resistant to other antibiotics (3, 4, 5, 6). For most species, the antibacterial effect is bacteriostatic, although it is bactericidal against most strains of Staphylococcus pneumoniae (13). In vitro combination studies with linezolid and several classes of antibiotics revealed indifference or additivity.

Linezolid is dosed intravenously or orally at 400 or 600 mg twice a day. Because the bioavailability of linezolid is approximately 100%, no dosage adjustment is needed when therapy is changed from the intravenous to the oral route (12). After the administration of oral 600-mg doses, steady-state peak concentrations in plasma (Cmax) of 21.2 ± 5.78 µg/ml are obtained at a time to Cmax (Tmax) of 1.03 ± 0.62 h. The plasma elimination half-life is 5.40 ± 2.06 h. Clearance occurs by both renal and nonrenal (65%) mechanisms and is moderately variable (80 ± 29 ml/min) at steady state with a dose of 600 mg twice daily. Linezolid is neutral in the physiological pH range and undergoes renal tubular reabsorption. The level of plasma protein binding is 31%, and the volume of distribution approximates the total body water content (40 to 50 liters) (9, 10; Zyvox package insert, Pharmacia Corporation, 2001). In a single-dose study, female human subjects had about 20% lower body weight-normalized clearances than males (Pawsey et al., Abstr. Eur. Congr. Antimicrob. Chemother., 1996). Linezolid is metabolized to two inactive metabolites, an amonoethoxyacetic acid metabolite (metabolite A) and a hydroxyethyl glycine metabolite (metabolite B).

Because a significant component of linezolid elimination is as unchanged drug in the urine, this study examined the single-dose pharmacokinetics of linezolid in male and female volunteers with various degrees of renal function to determine if dose adjustment is needed as a function of renal impairment. The renal functions of the subjects ranged from normal to severe chronic impairment, including end-stage renal disease (ESRD). Those with ESRD were maintained on hemodialysis.

MATERIALS AND METHODS

The pharmacokinetics of linezolid were determined following the administration of a single, oral dose of 600 mg of linezolid. The study was performed at the Kidney Disease Program of the University of Louisville, and the Human Studies Committee of the university approved its performance. Subjects provided written informed consent prior to entry into the study. An open-label, parallel-group design was used to study subjects with a range of renal functions, from normal to dialysis-dependent end-stage renal failure. Subjects who were maintained on hemodialysis were randomly studied twice: once during an intradialytic period and once during an interdialytic period. Subjects were recruited into one of four groups on the basis of their 24-h urinary creatinine clearance (Clcr) values or hemodialysis status: group 1, Clcr, >80 ml/min; group 2, Clcr, 40 to 80 ml/min; group 3, Clcr, 10 to 39 ml/min; group 4, hemodialysis. Subjects were excluded from study if they had a history of clinically significant organ dysfunction other than renal disease or those diseases associated with renal disease or if they had physical examination or laboratory test results outside the inclusion criteria. Female subjects were excluded if they were pregnant or lactating or were unwilling to use adequate contraceptive methods during the study and for 30 days following the study. Subjects were excluded for drug or alcohol abuse or if they tested positive for alcohol, drugs of abuse, hepatitis B or C virus, or human
immunodeficiency virus. Furthermore, subjects were excluded if they had taken an investigational drug within 2 months prior to enrollment in this study, CYP450 enzyme-altering agents within 30 days of doing so with the study medication, any new prescription drugs within 2 weeks of the study, and any nonprescription medication within 7 days of the study. Subjects were also excluded from the study if they had consumed alcohol, grapefruit, grapefruit juice, or tyramine-containing foods or beverages within 48 h of receiving study medication.

In the week prior to receiving the study medication, the subjects were screened for enrollment into the study. A physical examination and laboratory tests were performed to ensure that the subject met the inclusion and exclusion criteria. In those subjects that produced urine, a 24-h urine collection was performed to determine the subject’s CLCR. Subjects were enrolled in one of the study groups on the basis of this 24-h CLCR. The results of the 24-h CLCR were compared to an estimate of CLCR by use of the equation of Cockcroft and Gault (2). No measurement of CLCR was sufficiently different from the estimated CLCR to prompt a remeasurement of the CLCR.

On dialysis 12.4

TABLE 2. Linezolid pharmacokinetics in patients with different renal functions after administration of a 600-mg oral dose of linezolid

<table>
<thead>
<tr>
<th>Group</th>
<th>( C_{\text{max}} ) (μg/ml)</th>
<th>( T_{\text{max}} ) (h)</th>
<th>( AUC_{0-\infty} ) (μg · h/ml)</th>
<th>( t_{1/2} ) (h)</th>
<th>% of dose in urine</th>
<th>Clearance (ml/min)</th>
<th>Amt of drug (mg [%]) removed by hemodialysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oral</td>
<td>Renal</td>
<td>Oral</td>
</tr>
<tr>
<td>Group 1</td>
<td>12.7 ± 2.6</td>
<td>1.3 ± 0.8</td>
<td>110 ± 22</td>
<td>6.4 ± 2.2</td>
<td>31.1 ± 10.8</td>
<td>94.6 ± 21.8</td>
<td>27.9 ± 5.7</td>
</tr>
<tr>
<td>Group 2</td>
<td>15.5 ± 7.1</td>
<td>0.8 ± 0.4</td>
<td>128 ± 53</td>
<td>6.1 ± 1.7</td>
<td>28.5 ± 14.6</td>
<td>92.5 ± 43.9</td>
<td>21.2 ± 5.7</td>
</tr>
<tr>
<td>Group 3</td>
<td>10.8 ± 3.1</td>
<td>1.7 ± 1.1</td>
<td>127 ± 66</td>
<td>7.1 ± 3.7</td>
<td>9.8 ± 6.5</td>
<td>109.6 ± 77.5</td>
<td>7.4 ± 2.2</td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
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</tr>
<tr>
<td>Off</td>
<td>15.4 ± 5.0</td>
<td>0.9 ± 0.6</td>
<td>141 ± 45</td>
<td>8.4 ± 2.7</td>
<td>NA</td>
<td>76.6 ± 21.1</td>
<td></td>
</tr>
<tr>
<td>On</td>
<td>12.4 ± 4.1</td>
<td>1.0 ± 0.5</td>
<td>83 ± 23</td>
<td>7.0 ± 1.8</td>
<td>NA</td>
<td>130.0 ± 41.5</td>
<td>192 ± 47 (37 ± 3)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC<sub>0-∞</sub>, AUC from time zero to infinity; \( t_{1/2} \), apparent elimination half-life; NA, not applicable. The other abbreviations are defined in the text.
procedure with urine to also accurately quantitate the linezolid in the dialysate samples was conducted. Dialysate samples were included in two of the analytical runs with urine, and the results were successfully reported in the data report for urine.

Pharmacokinetic analysis of the data was performed by noncompartmental techniques. Plots of the data for all subjects were made by using Sigma-Plot software, with the data plotted as the log of the concentration versus time. All calculations were done with an Excel spreadsheet and validated by use of the Clinical Pharmacokinetics Analysis Package (version 1.0.39; Triology Consulting Corporation Clinical Pharmacokinetics Analysis Program, Version 1 User’s Manual, Triology Consulting Corporation, Kalamazoo, Mich., 1996). The terminal elimination phase of the plot was identified visually, and the elimination rate constant ($k_{el}$) was calculated by linear regression of these datum points. The elimination half-life was calculated as $\ln 2/k_{el}$. The area under the curve (AUC) was calculated by using the trapezoidal rule, and a tail correction was added to this area and was calculated as the last concentration above 0.2 µg/ml (LLOQ) divided by $k_{el}$. The total apparent oral clearance was calculated as the dose divided by the AUC. The renal clearance was calculated as the amount of parent drug recovered in the urine divided by the AUC. The nonrenal clearance was calculated as the difference between the apparent oral clearance and the renal clearance. The apparent volume of distribution was calculated as the oral dose times the area under the moment curve divided by AUC$^2$.

$T_{max}$ and $C_{max}$ were determined by inspection of the data. We calculated the extraction ratio across the dialyzer as the concentration in the venous blood sample divided by the concentration in the arterial blood sample for each of the additional arterial blood-venous blood sample pairs. The amount of drug removed during dialysis was determined by collecting a continuous sample of dialysate during the treatment. The total volume of dialysate processed was determined from the dialysate

FIG. 1. Plots of the mean serum linezolid concentration over time for the subjects, by group. Group 1, CLCr, >80 ml/min; group 2, CLCr, 40 to 80 ml/min; group 3, CLCr, 10 to 39 ml/min; group 4, hemodialysis patients.
flow rate (600 ml/min) and the length of the procedure. The amount removed was then the concentration in the dialysate times the volume processed.

Metabolite pharmacokinetic parameter estimates were calculated by noncompartmental methods. AUC was not extrapolated to infinity in patients with ESRD due to the lack of data for a sufficiently long period of time for accurate determination of a $k_{el}$ (the sampling time was limited to a total of 48 h postdosing due to the necessary dialysis schedule). Half-life data were estimated, but for the subjects with ESRD, these estimates have limitations due to the short sampling duration relative to the estimated half-life and should be interpreted with caution.

Statistical analysis of the data was performed with SPSS software (version 8.0). The data were analyzed by linear regression with analysis of variance by using the CLCR measured during the pharmacokinetic study as the independent variable. The data for the pharmacokinetic parameters for subjects in group 4 were tested for differences between the days off and on dialysis by a paired t-test.

RESULTS

Patient demographic parameters are shown in Table 1 The mean plasma linezolid concentration in each of the three groups with renal function and in hemodialysis subjects while they were not on dialysis are shown in Fig. 1 A plot of the mean linezolid concentrations in hemodialysis subjects while they were both on and off dialysis is found in Fig. 2 Pharmacokinetic parameters are summarized in Table 2 The AUC from time zero to infinity did not change over the range of renal functions tested. Likewise, the total apparent oral clearance of linezolid did not change with renal function and ranged from 92.5 to 109.6 ml/min in groups 1 to 3. For the subjects on dialysis, the total apparent oral clearance increased from 76.6 ml/min on their off-dialysis day to 130.0 ml/min on their on-dialysis day. The relationship between linezolid clearance and renal function as measured by CLCR is shown in Fig. 3 $k_{el}$ did not change with renal function. The half-life ranged from 6.1 to 8.4 h. The volume of distribution was not affected by renal function. Neither $T_{max}$ nor $C_{max}$ changed with renal function. Renal clearance showed a significant ($P < 0.0005$) decrease as renal function decreased. Four patients were dialyzed for 4 h, and the remaining two patients were dialyzed for 3 and 3.7 h, respectively. We were able to measure the amount of linezolid removed during the dialysis session in five of the six dialysis patients. On average, 192 mg of linezolid was removed during the dialysis session. The amount of drug extracted by the he-

![FIG. 2. Plots of mean serum linezolid concentrations over time for hemodialysis subjects while off dialysis and on dialysis.](image)

<table>
<thead>
<tr>
<th>TABLE 3. Metabolite A pharmacokinetics in patients with different renal functions after administration of a 600-mg oral dose of linezolid*</th>
<th>Group</th>
<th>$C_{max}$ (µg/ml)</th>
<th>$T_{max}$ (h)</th>
<th>AUC$_{0-7}$ (µg * h/ml)</th>
<th>$t_{1/2}$ (h)</th>
<th>% of dose in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>2.23 ± 0.38</td>
<td>6.0 ± 1.3</td>
<td>30.5 ± 6.2</td>
<td>6.6 ± 2.7</td>
<td>44.5 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>3.32 ± 2.44</td>
<td>6.7 ± 1.6</td>
<td>51.1 ± 38.5</td>
<td>9.9 ± 7.4</td>
<td>48.7 ± 11.9</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>8.64 ± 5.45</td>
<td>13.3 ± 4.3</td>
<td>203 ± 92</td>
<td>11.0 ± 3.9</td>
<td>34.5 ± 8.1</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
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</tr>
<tr>
<td>Off dialysis</td>
<td>14.0 ± 3.5</td>
<td>21.7 ± 9.5</td>
<td>467 ± 102</td>
<td>72 ± 34</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>On dialysis</td>
<td>7.00 ± 0.7</td>
<td>21.3 ± 9.9</td>
<td>239 ± 44</td>
<td>35 ± 22</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* Abbreviations: AUC$_{0-7}$, AUC from time zero to between 24 and 48 h after administration of the dose; $t_{1/2}$, apparent elimination half-life; NA, not applicable. The other abbreviations are defined in the text.
modiﬁcation was constant during the treatment and averaged 37% over the three additional arterial blood-venous blood sample pairs.

As shown in Tables 2, 3, and 4 and on the basis of CL\textsubscript{CR} as the measure of renal function, the concentrations of linezolid and both metabolites and the pharmacokinetic parameter estimates for linezolid and both metabolites were similar in those subjects with normal renal function (CL\textsubscript{CR}, >80 ml/min) and those subjects with moderate renal insufﬁciency (40 < CL\textsubscript{CR} < 80 ml/min). However, those subjects with severe renal insufﬁciency (CL\textsubscript{CR}, <40 ml/min) or those with ESRD maintained on hemodialysis had higher concentrations of both metabolites (Tables 3 and 4). With multiple dosing, the accumulation of both metabolites is likely in patients with severe renal insufﬁciency. Linezolid and the two metabolites are dialyzable, as the estimates of the C\textsubscript{max} of the metabolites and the AUC estimates were lower and the half-life estimates were shorter than the values for the same subjects without the 4-h dialysis session.

**DISCUSSION**

Vancomycin-resistant organisms are an important cause of infections in patients with renal disease, and linezolid is an effective treatment option for serious infections caused by drug-resistant gram-positive bacteria (1, 11). The appropriate use of antibiotics against vancomycin-resistant organisms in patients with impaired renal function requires detailed knowledge of the drug’s disposition in individuals who may have decreased drug clearance and the effects of dialysis on drug or metabolite removal.

We studied the elimination kinetics of linezolid in patients with renal insufﬁciency and on dialysis. We calculated linezolid clearance following oral administration of the drug. We are therefore reporting the apparent oral clearance of the drug that may be confounded with a bioavailability term; however, this is unlikely to be a signiﬁcant factor, considering the absorption properties of linezolid (complete absorption). As shown in Fig. 3, renal function has little effect on the overall clearance of the drug. In fact, despite a strong relationship between the renal clearance of the drug and CL\textsubscript{CR} (r^2 = 0.60; P < 0.001), total clearance did not fall as CL\textsubscript{CR} fell. This observation is accounted for by the increase in the nonrenal clearance seen as CL\textsubscript{CR} fell. In fact, some of the highest clearances occurred in subjects with CL\textsubscript{CR} below 40 ml/min. This apparent compensatory increase in nonrenal linezolid clearance could be the result of enhanced drug biotransformation, biliary excretion, decreased absolute bioavailability, or changes in drug distribution. For orally administered drugs, the volume of distribution is confounded by bioavailability and therefore cannot be accounted for separately.

Linezolid is a dialyzable drug, and a signiﬁcant portion of the dose could potentially be removed during a dialysis session, depending on the time of administration of the last dose in relation to the time of the hemodialysis session. A typical hemodialysis session occurs at a frequency of three times per week, with 48 to 72 h between the start of sessions. Therefore, there exists the potential for the elimination of a signiﬁcant portion of the dose in one of every four to six doses. Overall, linezolid elimination is not affected by renal function, and no dosage adjustment is warranted for patients with renal impairment. However, during the ﬁrst dialysis session of the treatment course, a supplemental dose of linezolid may be given if necessary to keep levels above the MIC for the organism causing the infection being treated.

The two major metabolites of linezolid were found to accumulate in patients with renal impairment, especially those with severe impairment or ESRD. This would not be unexpected, as both metabolites are almost exclusively eliminated in urine (10). The signiﬁcance of the metabolite accumulation is not fully understood at this time. However, it is known that the metabolites are qualitatively the same as those in preclinical safety evaluations of linezolid, although they are present at

![Regression plot of the oral linezolid clearance versus the measured CL\textsubscript{CR} at the time of dosing for all subjects in the study. The line represents the regression line of those data.](http://aac.asm.org/content/47/11/2779.full)

**TABLE 4. Metabolite B pharmacokinetics in patients with different renal functions after administration of a 600-mg oral dose of linezolid**

<table>
<thead>
<tr>
<th>Group</th>
<th>C\textsubscript{max} (µg/ml)</th>
<th>T\textsubscript{max} (h)</th>
<th>AUC\textsubscript{0-7} (µg · h/ml)</th>
<th>t\textsubscript{1/2} (h)</th>
<th>% of dose in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>0.76 ± 0.17</td>
<td>2.6 ± 1.2</td>
<td>7.57 ± 1.88</td>
<td>6.3 ± 2.1</td>
<td>15.0 ± 2.2</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.99 ± 0.30</td>
<td>3.3 ± 1.5</td>
<td>11.7 ± 4.3</td>
<td>6.6 ± 2.3</td>
<td>16.3 ± 4.4</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.61 ± 0.80</td>
<td>9.0 ± 3.3</td>
<td>56.5 ± 30.6</td>
<td>9.0 ± 4.6</td>
<td>13.0 ± 6.0</td>
</tr>
<tr>
<td>Group 4</td>
<td>6.07 ± 4.37</td>
<td>12.2 ± 7.2</td>
<td>185 ± 124</td>
<td>26.6 ± 21.4</td>
<td>NA</td>
</tr>
<tr>
<td>Off</td>
<td>3.25 ± 1.41</td>
<td>10.0 ± 10.8</td>
<td>68.8 ± 23.9</td>
<td>19.0 ± 10.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AUC\textsubscript{0-7}, AUC from time zero to between 24 and 48 h after administration of the dose; t\textsubscript{1/2}, apparent elimination half-life; NA, not applicable. The other abbreviations are deﬁned in the text.
lower concentrations than those expected with multiple dosing in humans. The metabolites also do not possess significant antimicrobial activity or a significant potential to inhibit various cytochrome P450 enzymes or monoamine oxidase. In addition, none of the more than 300 patients with severe renal impairment who have received linezolid either in phase III clinical trials or on a compassionate-use basis has shown any evidence of new types of adverse reactions or unacceptable tolerance, with the exception that the incidence of thrombocytopenia may be higher in patients with severe renal impairment. This is most likely due to the patients’ underlying characteristics (low baseline blood counts and longer-term treatments) and not due to the metabolites themselves. The clinical significance of metabolite accumulation is not yet fully elucidated and requires additional study with multiple doses in a controlled manner.

Hemodialysis is a significant source of elimination of linezolid and its two major metabolites in patients with end-stage renal failure. In this study, approximately one-third of the administered dose of the drug was removed by hemodialysis. In the experiments described here we used a high-flux or high-efficiency dialysis membrane comparable to others used in hemodialysis centers in the United States. Therefore, others should have the same experience that we did. Specifically, they should see an extraction of approximately 37% of the drug as it passes through the dialyzer. The amount removed depends on the proximity of the dialysis session in time to the time of dose administration. In our specific case, one-third of the dose was removed when dialysis was started 3 h following administration of the dose. A typical dialysis schedule of three treatments weekly would lead to an average weekly clearance of 100 ml/min, which is approximately the average for the other three renal function groups.

On the basis of these data, the dose of linezolid does not need to be altered for patients with impaired renal function. Because the drug is substantially removed by hemodialysis and to avoid potentially ineffective therapy, one of the twice-daily doses should be administered after the dialysis treatment on days when dialysis is performed.

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REFERENCES