Pharmacokinetics of Quinupristin-Dalfopristin in Continuous Ambulatory Peritoneal Dialysis Patients

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Quinupristin-dalfopristin may be useful for treatment of organisms causing peritoneal dialysis-related peritonitis, including methicillin-resistant coagulase-negative staphylococci, methicillin-resistant Staphylococcus aureus, and vancomycin-resistant enterococci. The pharmacokinetic profiles of single intravenous doses of this combination streptogramin antibiotic of 7.5 mg/kg of body weight were characterized for eight noninfected patients receiving continuous ambulatory peritoneal dialysis. Comparison was made to pharmacokinetic profiles determined for eight healthy volunteers matched by age, sex, and race. Drug was measured in dialysate up to 6 h following the dose. Plasma and dialysate were assayed for parent compounds and metabolites. Mean pharmacokinetic parameters were compared between groups. No statistically significant differences were observed between groups for maximal concentrations in plasma, times to maximal concentration, areas under the curve, distribution volumes, rates of total body clearance, or half-lives in plasma for quinupristin and dalfopristin. No statistically significant differences were observed in maximal concentrations in plasma, times to maximal concentration, areas under the curve, or half-lives for cysteine, the glutathione conjugates of quinupristin, or the pristinamycin IIA metabolite of dalfopristin. The measurements in dialysate of the parent and metabolites were below the expected MICs. Dialysis clearance was insignificant. Quinupristin-dalfopristin was well tolerated in both groups, causing only mild adverse events that resolved prior to discharge from the study. The disposition of quinupristin, dalfopristin, or their primary metabolites following a single dose was unaltered in patients receiving peritoneal dialysis. Intravenous dosing of this antibiotic combination is unlikely to be adequate for the treatment of peritonitis associated with peritoneal dialysis.

Antibiotic use continues to be common for patients receiving peritoneal dialysis. Peritonitis and catheter-related infections are frequent complications of this dialysis modality. Concerns over the emergence of methicillin- and vancomycin-resistant microorganisms have led to recent changes in treatment recommendations for these infections (6). Methicillin-resistant strains of Staphylococcus aureus and coagulase-negative staphylococci have been identified for many years in peritoneal dialysis patients. More recently, vancomycin-resistant Enterococcus faecium has been isolated from many patients receiving peritoneal dialysis. In addition, antibiotic-resistant strains are a growing cause of nosocomial infections (12). Quinupristin-dalfopristin, a new semisynthetic combination streptogramin, has shown activity in vitro and in vivo against many bacterial strains, including those with methicillin and vancomycin resistance (4, 10, 11, 13).

Quinupristin-dalfopristin (Synercid; Rhône-Poulenc Rorer) is the first injectable streptogramin. It is a combination of two semisynthetic derivatives of pristinamycin I and pristinamycin II in a fixed 30/70 ratio. The two components act synergistically against gram-positive organisms by inhibiting bacterial protein synthesis (1). The combination is usually bactericidal in vitro. The drug is not active against gram-negative bacilli.

Previous studies of healthy volunteers have been conducted to establish the pharmacokinetic parameters for quinupristin-dalfopristin. Following intravenous administration of 13C-quinupristin-dalfopristin, approximately 75% of the dose of drug-related components was excreted unchanged in the feces while less than 20% was recovered in the urine (5). Unchanged quinupristin accounted for 35% of total radioactivity of the pristinamycin I components excreted in the urine, and its main metabolite, a cysteine conjugate (RPR 100391), accounted for 38%. No unchanged dalfopristin was recovered in urine, but its metabolite pristinamycin IIA (RP 12536) represented 70% of total radioactivity of the pristinamycin II components excreted in the urine. RPR 100391 and RP 12536 possess in vitro antibacterial activities comparable to those of quinupristin and dalfopristin, respectively. The apparent elimination half-life (t1/2b) of each active compound was approximately 1.5 h for healthy volunteer subjects (3). Levels of protein binding of quinupristin and dalfopristin in healthy subjects were 23 to 32% and 50 to 56%, respectively (11a). The objectives of the present study were to characterize the pharmacokinetic profiles of quinupristin-dalfopristin in patients receiving continuous ambulatory peritoneal dialysis (CAPD), to determine the rate of antibiotic excretion into the peritoneal effluent, and to compare the pharmacokinetic parameters of quinupristin-dalfopristin in CAPD patients to those observed for healthy volunteers with normal renal function.
MATERIALS AND METHODS

Eight noninfected CAPD patients and eight healthy volunteers matched for sex, race, and age (±5 years) participated in this open-label, matched-control study. All participants were between the ages of 18 and 75 years, were not pregnant, and were within 25% of their ideal body weights. All CAPD patients had been receiving CAPD and had been peritonitis-free for at least 1 month. Patients were excluded if they smoked or if they had a positive serology result for hepatitis B, hepatitis C, or human immunodeficiency virus. Concomitant medications that might have affected hepatic microsomal enzymes were not allowed for 1 month prior to or during the study. All other medications routinely prescribed for dialysis patients were continued. All participants gave written informed consent. We obtained a baseline medical history and electrocardiogram and performed a physical examination and routine clinical laboratory testing prior to administration of the study drug. A clinical evaluation of each participant was repeated on the day of the study prior to drug administration and 10 h later upon completion of the study. All CAPD patients were studied in the General Clinical Research Center at the University of Wisconsin—Madison. Healthy volunteers were studied at the Corning Besselaar Clinical Research Unit, Inc. (Covance Clinical Research Unit, Inc.) in Madison, Wis.

Quinupristin-dalfopristin was given intravenously as a single dose of 7.5 mg/kg of actual body weight. The drug was administered with an infusion pump over 60 min in 250 ml of dextrose-5% water. All CAPD patients were subjected to a 1.5% dextrose dialysis exchange just prior to the start of drug dosing. The subsequent exchange was performed 6 h later.

Blood sampling. Two blood samples (4 ml each) were withdrawn from the arm opposite that receiving the drug infusion at the following times: time zero (prior to study drug administration); 15, 30, 60, 70, 80, 90, and 105 min after the start of infusion; and 2, 2.5, 3, 4, 5, 6, 8, and 10 h after the start of the infusion. Samples were withdrawn into two vacuum tubes, each of which contained 0.5 ml of 3.8% citrate. Immediately after collection, 9 ml of citrated blood was transferred into a tube containing 2 ml of 0.25 N hydrochloric acid kept on ice. The mixture was stirred gently by hand, and the tube was centrifuged immediately at 2,000 g and 4°C for 15 min. The resulting plasma supernatants were stored at −20°C.

Dialysate sampling. Dialysate effluent (50 ml) was withdrawn through the peritoneal dialysis catheter at 1.25, 2, 3, and 6 h following the start of the quinupristin-dalfopristin infusion. Buffer solution (5 ml, pH 3) was added immediately. Samples were stored at −20°C.

FIG. 1. Mean concentrations of quinupristin, RP 69012, and RPR 100391 in plasma versus time.

FIG. 2. Mean concentrations of dalfopristin and RP 12536 in plasma versus time.
The mean age for all participants was 43.6 years (range, 19 to 67 years). The mean weight for the CAPD patients was 72.2 kg (range, 60 to 104 kg); the mean height for all participants was 172.2 cm (range, 159 to 182 cm). There were 10 males (5 in each group) and 6 females (3 in each group). Potential participants were excluded if they exhibited any evidence of liver disease. Baseline blood pressures and heart rates were slightly higher in the CAPD patients and were lower than 17.7% and accuracy was between 90.7 and 114.3%.

Pharmacokinetic analysis. Noncompartmental pharmacokinetic analysis was performed with WinNonlin, version 1.1 (Pharnight of North Carolina). The maximum concentration of drug in plasma ($C_{\text{max}}$) and the time at which $C_{\text{max}}$ occurred ($t_{\text{max}}$) were determined from the experimental concentration-time curve in plasma. The area under the concentration-time curve (AUC) in plasma was calculated by dividing the dose by the product of the terminal concentration-time data. The apparent volume of distribution ($V_{\text{app}}$) was calculated with the equation $V_{\text{app}} = D/AUC_{\infty}$, where $D$ is the dwell volume of dialysate, $C_{\text{i}}$ is the dialysate drug concentration, and $i$ is the dwell time. CL from plasma and $V_{\text{app}}$ were not calculated for the metabolites RP 69012, RPR 100391, and RP 12536.

RESULTS

Patient demographics. The mean age for all participants was 43.6 years (range, 19 to 67 years). The mean weight for the CAPD patients was 72.2 kg (range, 60 to 104 kg); the mean height for all participants was 172.2 cm (range, 159 to 182 cm). There were 10 males (5 in each group) and 6 females (3 in each group). Potential participants were excluded if they exhibited any evidence of liver disease. Baseline blood pressures and heart rates were slightly higher in the CAPD patients and were lower than 17.7% and accuracy was between 90.7 and 114.3%.

Pharmacokinetics. The mean concentration-time profiles in plasma for quinupristin, RPR 100391, and RP 69012 are presented in Fig. 1. Quinupristin concentrations could not be determined accurately for CAPD patients 2 and 3 due to suspected interference with furosemide in the plasma. The mean concentration-time profiles in plasma for dalfopristin and pristinamycin IIA are presented in Fig. 2. The pharmacokinetic parameters are presented in Tables 1 and 2. The peak concentrations of all metabolites in plasma were achieved at nearly the same time as the peak concentrations of the parent compounds in plasma for both healthy volunteers and CAPD patients. Mean total CL from plasma for both parent compounds was high for each group of study participants. There was no statistically significant decrease in CL from plasma or $V$ values for the CAPD patients compared to values for the healthy subjects for either quinupristin or dalfopristin. Moderate increases in the $AUC_{\infty}$ values for quinupristin (+18%) and dalfopristin (+29%) were observed for the CAPD patients compared to those for the healthy volunteers; however, these differences were not statistically significant. The $AUC_{\infty}$ values of the metabolites were comparable in both groups. Dalfopristin and a glutathione conjugate of quinupristin (RP

<table>
<thead>
<tr>
<th>Group</th>
<th>Quinupristin (RP 57669)</th>
<th>Dalfopristin and its metabolites</th>
<th>RPR 100391 (glutathione conjugate)</th>
<th>RP 69012 (cysteine conjugate)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$ (mg/ml)</td>
<td>$t_{\text{max}}$ (h)</td>
<td>AUC$_{\text{0–t}}$ (mg·h/ml)</td>
<td>$t_{1/2}$ (h)</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volunteers</td>
<td>2.60 ± 0.43</td>
<td>1.44 ± 0.50</td>
<td>0.65 ± 0.26</td>
<td>0.72 ± 0.25</td>
</tr>
</tbody>
</table>
| Values are means ± SD. Differences between values were not statistically significant ($P > 0.05$).
that following a 1-h infusion, quinupristin and dalfopristin un-
sea.
but three of the healthy volunteers did. Five of the CAPD
patients and one healthy volunteer experienced pain at the
mild, and they resolved prior to discharge from the study. Six
volunteer group, as noted in Table 3. All adverse events were
adverse events, 28 in the CAPD group and 6 in the healthy
any of the laboratory parameters from baseline through study
the peritoneal fluid was estimated.
the very low rate of dialysate CL for all the compounds, no rate
tin, and their respective metabolites were negligible. Due to
0.28 liter/h). Peritoneal CL values for quinupristin, dalfopris-
tion. The dialysate RPR 100391 concentrations were low com-
below those observed in plasma. A mean C_{max} of 0.207 µg/
ml in dialysate was reached at 2 h compared to that of 0.974
µg/ml in plasma at the end of infusion. Dialysate pristinamycin
IA concentrations at 6 h were nondetectable. The cysteine
conjugate of quinupristin (RPR 100391) appeared slowly in
dialysate, reaching a mean C_{max} at 6 h after the start of infu-
sion. The dialysate RPR 100391 concentrations were low com-
pared to those observed in plasma. RPR 100391 was the only
compound for which peritoneal CL could be calculated (0.56 ±
0.28 liter/h). Peritoneal CL values for quinupristin, dalfopris-
tin, and their respective metabolites were negligible. Due to
the very low rate of dialysate CL for all the compounds, no rate
of appearance of the intravenously administered product into
the peritoneal fluid was estimated.

**Safety results.** There were no clinically significant changes in
any of the laboratory parameters from baseline through study
termination 10 h after the start of infusion. There were 34
adverse events, 28 in the CAPD group and 6 in the healthy
volunteer group, as noted in Table 3. All adverse events were
mild, and they resolved prior to discharge from the study. Six
patients and one healthy volunteer experienced pain at the
infusion site. No patients had inflammation at the infusion site,
but three of the healthy volunteers did. Five of the CAPD
patients, but none of the healthy volunteers, experienced nau-
sea.

**DISCUSSION**

Previous studies of healthy volunteers have demonstrated that
following a 1-h infusion, quinupristin and dalfopristin un-
dergo rapid elimination, with t_{1/2b} values of about 1 h. Approx-
imately 75% of the dose of each compound is fecally excreted.
Less than 20% of the dose is excreted in the urine as either
parent drug or metabolites (5). In a previous study of intrave-
nous quinupristin-dalfopristin given to patients with severe
chronic renal failure, the disposition profiles of quinupristin
were comparable in patients with severe renal failure and in
healthy volunteers. However, the elimination of quinupristin
metabolites may have been somewhat impaired, as indicated
by selective bioassay. The elimination of dalfopristin was slight-
ly modified in the renal-failure patients. The mean C_{max} and
AUC_{0–\infty} values for dalfopristin were about 1.3 times higher
than those estimated for healthy volunteers (11a).

For quinupristin and dalfopristin, the results of the present
study are consistent with the results of the earlier study of
patients with chronic renal failure. While not statistically sig-
nificant, the slight-to-moderate increases in AUC_{0–\infty} values in
plasma suggest that nonrenal CL of these compounds may be
slightly reduced in patients undergoing CAPD. The pharma-
cokinetic parameters for the metabolites in our study showed
some differences compared to those of the earlier study of
chronic renal failure. In the earlier study, statistically signifi-
cant increases were observed in the AUC_{0–\infty} values of qui-
numpristin and active metabolites, as determined by bioassay,
suggesting an increase of quinupristin metabolite concentrations.
In the present study, no differences in AUC_{0–\infty} values for qui-
umpristin metabolites were observed between CAPD patients
and healthy volunteers. This difference between the two stud-
ies may be explained by differences in analytical techniques
used (bioassay versus high-performance liquid chromatogra-
phy) or by the contribution of CL via peritoneal dialysis. This
latter hypothesis seems unlikely given the molecular weights of
quinupristin and its metabolites. The pharmacokinetic param-
eters observed in the present study for the healthy volunteers
were similar to those seen in previous studies with volunteer
groups.

Patients receiving peritoneal dialysis may develop commu-
nity-acquired or nosocomial infections for which quinupristin-
dalfopristin may be indicated. The results of this study indicate
that peritoneal CL of both drugs and their metabolites is a
relatively insignificant contributor to total body CL. Because
insignificant amounts of both parent drugs and their metabo-
lites are excreted into dialysis effluent, intravenous dosing of
quinupristin and dalfopristin is unlikely to be adequate for the
treatment of peritoneal dialysis-related peritonitis. While the
data from this study suggest that dose adjustments will not be
required for intravenous administration to patients receiving
CAPD, future multiple-dose studies will need to confirm dosing
recommendations for therapeutic use. Currently, there are
no data regarding the intraperitoneal dosing of this antibiotic
combination.

**TABLE 3. Adverse events observed during the study**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>No. of patients</th>
<th>No. of volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiff neck</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Coughing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Arm, hand, and/or shoulder stiffness</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Metallic taste</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Numbness in nose</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Emetism</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Numbness in lips</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tingling in shoulders</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Burning or discomfort at i.v. site</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Aching arm above i.v. site</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Erythema in arm at i.v. site</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

* i.v. site, site of intravenous injection.

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**TABLE 2. Pharmacokinetic parameters of dalfopristin and its metabolite RP 12536**

<table>
<thead>
<tr>
<th>Group</th>
<th>C_{max} (µg/ml)</th>
<th>t_{max} (h)</th>
<th>AUC_{0–\infty} (µg h/ml)</th>
<th>CL (liter/h · kg)</th>
<th>V (liter/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>8.52 ± 3.52</td>
<td>1</td>
<td>9.72 ± 4.53</td>
<td>0.67 ± 0.36</td>
<td>0.68 ± 0.30</td>
</tr>
<tr>
<td>Volunteers</td>
<td>7.09 ± 2.70</td>
<td>1</td>
<td>7.60 ± 2.81</td>
<td>0.77 ± 0.30</td>
<td>0.77 ± 0.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>C_{max} (µg/ml)</th>
<th>t_{max} (h)</th>
<th>AUC_{0–\infty} (µg h/ml)</th>
<th>CL (liter/h · kg)</th>
<th>V (liter/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>0.974 ± 0.32</td>
<td>1</td>
<td>1.62 ± 0.48</td>
<td>0.84 ± 0.39</td>
<td>0.36 ± 0.68</td>
</tr>
<tr>
<td>Volunteers</td>
<td>1.05 ± 0.29</td>
<td>1</td>
<td>1.54 ± 0.28</td>
<td>1.15 ± 0.23</td>
<td>0.29 ± 0.67</td>
</tr>
</tbody>
</table>

* Values are means ± SD. Differences between values were not statistically significant (P > 0.05).
ACKNOWLEDGMENTS

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REFERENCES


