Pharmacokinetics of Gentamicin in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

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The pharmacokinetics of gentamicin were studied in seven chronic renal failure patients undergoing continuous ambulatory peritoneal dialysis. Patients received 100 mg of gentamicin in 2 liters of dialysate during an initial pass, and serum and dialysate samples were collected for gentamicin determination. Approximately 49% of the amount introduced into the peritoneal cavity was absorbed systemically during a 6-h cycle. Subsequent clearance of gentamicin from the serum occurred slowly with an elimination half-life of 36 h. Dialysis clearance of gentamicin during continuous ambulatory peritoneal dialysis was 2.94 ml/min.

Peritonitis is a frequent and potentially serious complication of continuous ambulatory peritoneal dialysis (CAPD). Rubin et al. (2) have reported an incidence of 6.3 episodes per patient year. Although the most frequently isolated organisms are staphylococci, infection with gram-negative organisms occurs in 15% of the cases (2).

These infections often require the use of an aminoglycoside antibiotic intraperitoneally. Patients whose infections become systemic then require intravenous antibiotic treatment. Smithivas and co-workers (4) suggested treating peritonitis in patients undergoing intermittent peritoneal dialysis with gentamicin added to the dialysis fluid. Concentrations equal to those desired in the serum of septic patients were recommended. Equilibration of the drug with the serum usually required a period of 12 h, and for this reason the authors suggested the additional administration of intramuscular gentamicin.

The pharmacokinetics of most drugs during CAPD have not been widely studied. The rate and extent of systemic absorption from the intraperitoneal administration of gentamicin with this new technique have not been investigated nor have the rate and extent of removal of gentamicin from the blood by this type of dialysis.

In view of the fact that the removal of small and middle molecules (molecular weight less than 5,000) with CAPD has been found to be significantly different from their clearance by hemodialysis or intermittent peritoneal dialysis (1), it was our objective to characterize the pharmacodynamics of gentamicin after intraperitoneal administration in patients undergoing CAPD.

MATERIALS AND METHODS

Seven patients with chronic renal failure undergoing CAPD volunteered to enter the study. Each patient received 100 mg of gentamicin which had been added to a 2-liter bag of peritoneal dialysate (1.5% dextrose). The contents of the bag were infused into the peritoneal cavity over a measured period of time (5 to 10 min). Samples (10 ml) of the peritoneal dialysate were collected aseptically immediately after the infusion and 1, 3, and 6 h later. Three blood samples (4 ml) were collected 1, 3, and 6 h after intraperitoneal administration of the drug. At the end of the 6 h, the peritoneal dialysate was drained into the empty 2-liter plastic bag and labeled, and 2 liters of fresh peritoneal dialysate was introduced into the peritoneal cavity. This process was repeated every 6 h for eight additional exchanges. In addition, blood samples were collected from five patients at 12, 24, and 48 h after the administration of the drug.

The concentration of gentamicin in blood and peritoneal fluid was determined by radioimmunoassay (New England Nuclear Corp., Boston, Mass.).

The total amount of gentamicin absorbed from the peritoneal cavity was calculated by subtracting the amount of gentamicin still remaining in the bag at the end of the 6-h equilibration period from the initial dose introduced into the bag (100 mg). The volume of distribution was calculated from the formula: 

\[ V_{D} = \frac{A}{C_{p}} \]

where \( V_{D} \) = volume of distribution, \( A \) = amount absorbed (mg), and \( C_{p} \) = peak blood concentration obtained during the 6 h of intraperitoneal administration. The elimination rate constant (\( k_{e} \)) was obtained by linear regression analysis of the blood level data collected after the 6-h time period. The half-life was then calculated as \( 0.693/k_{e} \).

The dialysis clearance (\( CL_{D} \)) was obtained from the formula:

\[ CL_{D} = \frac{A_{d} \cdot 48}{\int_{0}^{48} C_{p} \, dt} \]
where $A_d$ | % is the amount of the drug collected in the dialysate from the 6-h drainage until 48 h later, and $f_{\text{D}}\text{Cptd}$ is the area under the plasma concentration curve (obtained by using the trapezoidal rule) during the same time interval.

Because of technical difficulties with the placement of the catheter resulting in incomplete recovery of the dialysis fluid, the dialysis clearance was calculated in only four patients.

The calculation of the volume of distribution and the dialysis clearance assumes no elimination of drug through renal or nonrenal mechanisms. This assumption is valid since all patients in the study produced little or no urine during the study period and gentamicin is known to undergo no elimination through metabolism.

**RESULTS**

Clinical data for each patient are shown in Table 1. Patients were either anephric or virtually anuric with daily urine volumes of less than 50 ml. The pharmacokinetic data are shown in Table 1. Blood gentamicin levels rose rapidly during the first hour and were still rising at the end of the 6-h equilibration period. Extrapolation of the lines for gentamicin concentration in blood and peritoneal fluid suggests that complete equilibration would take about 48 h (Fig. 1). Approximately 49% of the administered dose was absorbed during the 6-h equilibration period. The mean peak serum gentamicin concentration was 3.9 $\mu$g/ml (range 2.4 to 6.2 $\mu$g/ml). The mean dialysis clearance of gentamicin from the blood by CAPD was 2.94 ml/min. This resulted in the removal of 20.2% of the absorbed gentamicin over a 24-h period by CAPD.

The mean concentration of gentamicin in the peritoneal dialysate and the corresponding serum concentration are plotted logarithmically as shown in Fig. 1. During the equilibration period while gentamicin was still in the peritoneal cavity, the mean half-life for transfer of the drug from the peritoneum to the blood was 5.6 h. The average half-life for elimination of gentamicin from the serum after the equilibration period was calculated to be 36 h, ranging from 27.7 to 50.4 h in the five patients studied.

**DISCUSSION**

Our study shows that gentamicin is rapidly absorbed from the peritoneal cavity in patients undergoing CAPD with approximately 49% of the administered dose of gentamicin being absorbed over a 6-h period. Nevertheless, final equilibration between blood and peritoneal fluid would probably take as long as 48 h. This is in contrast to the pharmacokinetics of gentamicin in patients undergoing intermittent peritoneal dialysis where other investigators have reported that equilibration occurs in 12 h (4). Our results indicate that therapeutic levels of gentamicin can be rapidly achieved in the blood of CAPD patients by adding the appropriate dosage of gentamicin to the peritoneal dialysate. In our study, an arbitrary dose of 100 mg of gentamicin produced average peak serum concentrations of 3.9 $\mu$g/ml during a 6-h equilibration period. On a weight-for-weight basis, this was an average dose of 1.42 mg/kg of body weight. Therapeutic blood levels of 5 $\mu$g/ml could be produced by adding 135 mg of gentamicin to the 2-liter bag of peritoneal dialysate. Higher doses could be utilized when higher serum concentrations are desired.

The volume of distribution (0.20 liter/kg) observed in CAPD patients appears to be similar to that reported in patients with normal renal function (3). The half-life for elimination of the drug from the serum (36 h) indicates a very slow clearance of the drug from the serum in CAPD patients. This is also evident from the low dialysis clearance measured in our patients, 2.94 ml/min, and by the percentage of drug absorbed

**Table 1. Clinical and pharmacokinetic data**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Wt (kg)</th>
<th>BUN (mg/dl)</th>
<th>SrCr (mg/dl)</th>
<th>Amt absorbed (%)</th>
<th>Peak ((\mu)g/ml)</th>
<th>V_D (liter/kg)</th>
<th>K_d (h^-1)</th>
<th>t_1/2 (h)</th>
<th>CL_D (ml/min)</th>
<th>% Removed in 24 h</th>
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<td>3.26</td>
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<td>2</td>
<td>27</td>
<td>65.1</td>
<td>41</td>
<td>12.8</td>
<td>57.5</td>
<td>4.2</td>
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<td>75</td>
<td>10.3</td>
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<td>10.5</td>
<td>47.3</td>
<td>5.1</td>
<td>0.15</td>
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<td>—</td>
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<tr>
<td>7</td>
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<td>74</td>
<td>12.5</td>
<td>67.6</td>
<td>6.2</td>
<td>0.33</td>
<td>0.022</td>
<td>31.5</td>
<td>2.72</td>
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<tr>
<td>Mean</td>
<td>54.0</td>
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<td>67.0</td>
<td>12.7</td>
<td>49.0</td>
<td>3.9</td>
<td>0.22</td>
<td>0.020</td>
<td>36.0</td>
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<td>2.5</td>
<td>14.7</td>
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<td>6.9</td>
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*Abbreviations: Pt, patient; BUN, blood urea nitrogen; SrCr, serum creatinine; V_D, volume of distribution; K_d, elimination rate constant; t_1/2, half-life; CL_D, dialysis clearance; —, not done.
removed per 24 h of CAPD. Our data suggest that over 48 h of CAPD would be necessary to remove 50% of the amount of gentamicin found in the body.

In conclusion, our investigation demonstrates that gentamicin is rapidly absorbed from the peritoneum of patients undergoing CAPD and that removal from the blood consequently proceeds at a very low rate. Our results also suggest that when therapeutic serum gentamicin concentrations are desired, the addition of 135 mg of gentamicin to the first dialysis bag will produce serum gentamicin concentrations above 5 μg/ml within 6 h.

Patients not requiring rapid attainment of therapeutic serum concentrations of gentamicin should receive 30 mg of gentamicin in each 2-liter bag for at least 48 h. This should produce concentrations of gentamicin in the peritoneal fluid fluctuating between 15 and 7.5 μg/ml during each 6-h cycle. After 48 h when equilibration has been completed, passes should be made with fluid containing 5 to 10 μg of gentamicin per ml per bag to maintain therapeutic concentrations in the infected peritoneum. It should be kept in mind that after equilibration is completed, patients will maintain serum concentrations of gentamicin for prolonged periods of time and that the potential for ototoxicities may therefore be increased.

LITERATURE CITED