Pharmacokinetics of Amikacin During Hemodialysis and Peritoneal Dialysis

LISBETH REGEUR, HANNE COLDING,* HERLUF JENSEN, AND JENS P. KAMPMANN

Department of Clinical Bacteriology, Clinical Pharmacology Research Unit, Medical Department P, Division of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

Received for publication 21 September 1976

The pharmacokinetics of amikacin were examined in six bilaterally nephrectomized patients undergoing hemodialysis and in four patients with a minimal residual renal function undergoing peritoneal dialysis. The mean elimination half-life before the dialysis was 86.5 h in the anephric patients and 44.3 h in the patients with minimal residual kidney function. The results from the anephric patients suggest that some extrarenal elimination of amikacin may occur. The mean volume of distribution was about 25% of the total body weight. This is in accordance with values reported from subjects with normal renal function. During hemodialysis the half-life decreased to less than 10% (5.6 h) of the pretreatment value. The effectiveness of peritoneal dialysis was less as the half-life decreased to only about 30% (17.9 h) of the pretreatment value. During the dialyses a significant correlation between the half-life of amikacin and the decrease in blood urea and serum creatinine was demonstrated. The pharmacokinetic data were used to make dosage regimen recommendations for the treatment of patients undergoing intermittent hemodialysis or peritoneal dialysis.

Amikacin is a new semisynthetic aminoglycoside antibiotic with kinetics and toxicity similar to those of kanamycin (4, 5, 7). The antimicrobial activity differs, however, as amikacin is active against various isolates of gram-negative bacilli resistant to other aminoglycosides including kanamycin, gentamicin, and tobramycin (10, 12, 17).

Severe bacterial infections are common in uremic patients, and treatment with aminoglycosides is often required. Like other aminoglycosides, amikacin is mainly eliminated by glomerular filtration of the unchanged drug, and a correlation between the elimination half-life and the serum creatinine concentration in patients with varying degrees of reduced renal function has recently been demonstrated (13, 15).

The purpose of the present study has been to evaluate the kinetics of amikacin in bilaterally nephrectomized patients undergoing hemodialysis and in patients with minimal residual renal function undergoing peritoneal dialysis. The kinetics have been investigated both before and during the dialyses.

MATERIALS AND METHODS

Patients. Ten patients, five females and five males, were studied. Their ages ranged from 23 to 58 years, and their weights ranged from 41 to 76 kg. All of the patients had terminal renal insufficiency that required regular treatment with dialysis. Six of the patients were nephrectomized bilaterally and treated with intermittent hemodialysis. The other four patients had an endogenous creatinine clearance between 2.8 and 4.9 ml/min and were treated with intermittent peritoneal dialysis. All patients were treated as outpatients, and they were in reasonably good health during the study. The weight varied maximally 4.3% during the dialyses and not more than 2.9% between the dialyses. The patients did not receive any other medication during the study. None of the patients suffered from edema or ascites.

Informed consent was obtained from each patient after an explanation of the risks and inconveniences reasonably to be expected.

Dialysis. The hemodialysis was performed twice weekly over 7 to 10 h. In five cases a plate kidney (type Gambro-Lundia Optima; 17 μm) was used, and in one case (see Table 1, patient no. 2) a capillary kidney (Cordis Dow model 4) was used. The peritoneal dialysis was performed once weekly with a Tenckhoff catheter, using about 60 liters of dialyzing fluid over a period of about 30 h.

Administration of antibiotic. A 125-mg amount of amikacin dissolved in 200 ml of isotonic saline was infused intravenously over a period of 1 h in all patients immediately after dialysis (1.7 to 3.1 mg/kg). Blood samples for the determination of amikacin, creatinine, and urea were drawn 1 h after termination of the infusion and once or twice daily until the next dialysis. During the hemodialysis, four blood samples were taken every 2 to 3 h, beginning at the onset of the dialysis. In patients un-
diseases undergoing peritoneal dialysis five samples were drawn every 5 to 6 h.

Antibiotic assay. The serum concentration of amikacin was measured microbiologically with filter paper disks (19). A laboratory strain of Bacillus subtilis was used as the test organism. The intra- and interassay variation was below 5%.

Data analysis. The pharmacokinetic parameters were calculated according to an open one-compartment model.

(i) Elimination half-life. Elimination half-life was obtained from the linear part of the curve of log concentration versus time by a least-squares regression.

(ii) Apparent volume of distribution. Apparent volume of distribution was calculated by dividing the dose given with the extrapolated zero concentration obtained in the period before the dialysis.

(iii) Total body clearance of amikacin. Total body clearance of amikacin was calculated from the above data according to the formula: clearance = (0.693 \cdot V_a) / T_{1/2}, where V_a is the apparent volume of distribution and T_{1/2} is the elimination half-life. In the model used, both the volume of distribution and clearance are slightly overestimated. The error, however, is minor because of the very rapid tissue distribution of all aminoglycosides.

The data were subjected to statistical evaluation, using Student's t test and linear correlation analysis.

RESULTS

The measured and calculated parameters are shown in Table 1. The mean elimination half-life was 86.5 h (range, 56.1 to 150.6 h) in the six anephric patients and 44.3 h (range, 33.5 to 49.9 h) in the four patients with minimal residual renal function. The total body clearance was 1.6 ± 0.5 and 2.5 ± 0.4 ml/min (mean ± standard deviation) in the two groups, respectively. These differences are significant (P < 0.05).

The mean volumes of distribution expressed as a percentage of the total body weight were 28.1 and 25.8%, respectively. No significant difference was found between these two values (P > 0.05).

During dialysis the half-lives decreased and the total body clearances increased significantly (P < 0.01) in both groups. In the patients hemodialyzed the half-life decreased to a mean value of 5.6 h (range, 4.1 to 7.3 h), and in the group subjected to peritoneal dialysis it decreased to a mean value of 17.9 h (range, 13.6 to 21.1 h). The increase in serum creatinine and blood urea before the dialyses equalled the decrease resulting from the dialyses (P > 0.05).

Figure 1 shows the logarithmic decline of the serum concentrations of amikacin in the individual patients. After an initial phase of distribution the mean serum concentration was 8.1 μg/ml in the group undergoing hemodialysis (mean body weight, 55.2 ± 11.5 kg) and 5.9 μg/ml in the group undergoing peritoneal dialysis (mean body weight, 67.2 ± 6.3 kg). Immediately before the next dialysis the values had decreased to 5.1 and 2.9 μg/ml, respectively. After termination of the dialysis the mean value of amikacin in the patients treated with hemodialysis was 2.0 μg/ml (a decrease of 61%), whereas the patients treated with peritoneal dialysis had a mean value of 0.8 μg/ml (a decrease of 72%).

Figures 2 and 3 show a significant inverse correlation between the half-life of amikacin during the dialysis and the decrease in the concentrations of serum creatinine and blood urea, respectively (r = −0.89 and −0.71; P < 0.05).

DISCUSSION

The present study shows that amikacin in common with other aminoglycosides has a prolonged half-life in patients with reduced renal function. Although most of the drug is excreted unchanged by the renal route, the decay of the serum concentration in six patients without kidneys shows that some extrarenal elimination may occur. In accordance with this finding, only about 90% of a parenteral dose is recovered in urine (7). A comparison between the anephric patients and the patients with minimal residual renal function shows that even an endogenous creatinine clearance of about 3 ml/min results in a significantly lower half-life of amikacin in the latter group. The average serum concentration of creatinine before dialysis in the four patients on peritoneal dialysis was about 12 mg/100 ml, and the measured average half-life of 44.3 h is in good agreement with the values presented by Levy and Klaster ski (13). A volume of distribution of about 0.25 liter/kg is in accordance with the values reported from subjects with normal renal function (4, 5), indicating that the delayed excretion does not influence the distribution of the drug.

The pharmacokinetics of the aminoglycosides during dialysis have been reported in several works (1, 6, 8, 9, 14). It has been shown that the serum concentrations of kanamycin, gentamicin, and tobramycin decreased more than 70% during an 8- to 10-h period of hemodialysis (Kii dialyzer), and during peritoneal dialysis the serum concentrations of kanamycin and tobramycin have been shown to decrease 32 and 65% during 22 and 12 h of dialysis, respectively (2, 16).

The present study shows that amikacin is also substantially cleared from the body of anephric patients during hemodialysis, with a de-
## Table 1. Pharmacokinetic parameters of amikacin before and during hemodialysis and peritoneal dialysis

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>V_d (%) (% of total body weight)</th>
<th>Before dialysis</th>
<th>During dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V_d (h)</td>
<td>Clearance of amikacin (ml/min per m²)</td>
<td>Increase in blood urea (mmol/liter)</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1</td>
<td>34.3</td>
<td>56.1</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>79.9</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>6</td>
<td>24.6</td>
<td>85.6</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.1 ± 6.7</td>
<td>86.5 ± 30.7</td>
<td>1.6 ± 0.5</td>
</tr>
</tbody>
</table>

**Peritoneal dialysis**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>V_d (%) (% of total body weight)</th>
<th>Before dialysis</th>
<th>During dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V_d (h)</td>
<td>Clearance of amikacin (ml/min per m²)</td>
<td>Increase in blood urea (mmol/liter)</td>
</tr>
<tr>
<td>7</td>
<td>21.3</td>
<td>49.0</td>
<td>1.9</td>
</tr>
<tr>
<td>8</td>
<td>32.1</td>
<td>44.7</td>
<td>3.0</td>
</tr>
<tr>
<td>9</td>
<td>27.9</td>
<td>49.9</td>
<td>2.3</td>
</tr>
<tr>
<td>10</td>
<td>21.7</td>
<td>33.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>25.8 ± 4.5</td>
<td>44.3 ± 6.5</td>
<td>2.5 ± 0.04</td>
</tr>
</tbody>
</table>

*V_d,* Apparent volume of distribution.

*SD,* Standard deviation.
crease in half-life to less than 10% of the pretreatment values, approaching the value of 2 h in humans with normal kidney function (4, 5). The effectiveness of peritoneal dialysis is less as the half-life is decreased to only about 30% of the pretreatment value.

The serum concentration of amikacin prior to dialysis was 3 to 6 μg/ml in most of the patients. The highest concentrations were found in patients on hemodialysis, which is to be expected from the smaller total body weight. After dialysis the concentration decreased to levels less than 2 μg/ml, which is below the minimum inhibitory concentration for various isolates of bacterial strains (11). The toxic peak serum level of amikacin has recently been shown to be close to the value given for kanamycin, i.e., about 30 μg/ml (3). A dose of 5 to 7 mg/kg of body weight administered intravenously immediately after dialysis will result in serum concentrations of about 20 μg/ml, well above the minimum inhibitory concentration, but below the toxic level. With a serum half-life in anephric patients of about 3 days, this dose will suffice until the next dialysis, even if dialysis is performed only once weekly. In patients with minimal residual renal function (i.e., endogenous creatinine clearance between 2 and 5 ml/min) the half-life is about 2 days, and one extra dose after 4 days may well be necessary.
During dialysis a significant correlation between the half-life of amikacin and the decrease in blood urea and serum creatinine was demonstrated. This finding differs from a previous observation concerning gentamicin and kanamycin (9), but is in agreement with Riff and Jackson (18), who demonstrated a significant correlation between the degree of dialysis of creatinine and gentamicin during hemodialysis. However, the studies are not directly comparable as different kinds of artificial kidneys were used.

It is obvious that large individual differences exist regarding the various kinetic parameters of amikacin. The dose schedule suggested is therefore only to be considered as a clinical guideline and should be supplemented with serum concentration measurements whenever possible.

LITERATURE CITED