Administration of Aminoglycosides to Hemodialysis Patients: a New Dosing Modality

HIDENORI MATSUO,1* JUNICHI HAYASHI,1 KUMEO ONO,1 KIMIKO ANDOH,1 YOSHITAKA ANDOH,1 YOSHIKI SANO,2 KAZUHIISA SARUKI,3 JUNSUKE TANAKA,4 MAMORU YAMASHITA,4 KAZUNORI NAKAMURA,5 AND KAZUO KUBO1

Dialysis Center,1 Department of Surgery,2 and Department of Urology,3 Hidaka Hospital, Takasaki, Gunma Prefecture, Department of Acute Medicine,4 Tsukuba University, Tsukuba, Ibaraki Prefecture; and Department of Nephrology,5 Tokyo Women’s Medical College, Tokyo, Japan

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We describe a new modality for administering aminoglycosides to hemodialysis (HD) patients, namely, a modification of the once-daily regimen which consists of administering the aminoglycosides over 60 min by drip infusion just before each HD session, with a preplanned peak concentration being reached at the beginning of the session and then with a rapidly decreasing concentration being achieved by the start of HD. The area under the concentration-time curve (AUC), i.e., the accumulation of the drug in the body, is thus minimized by this modality. Arbekacin (ABK) was given at a dose of 2 mg/kg of body weight to 10 HD patients infected with methicillin-resistant Staphylococcus aureus (MRSA) for 2 weeks (six sessions in total), resulting in the complete disappearance of MRSA in 5 patients. A high rate of elimination of ABK was attained for each patient while the patient was on HD (range, 0.20 to 0.42 h−1; mean, 0.28 ± 0.08 h−1) by using high-performance dialyzers provided with membranes made of either polymethylmethacrylate, cellulose triacetate (CTA), or ethylene vinyl alcohol. The best results were obtained with the CTA membrane, as revealed by the overall mass transfer coefficient (Kt).

The concept of once-daily aminoglycoside dosing is based mainly on the short time- and concentration-dependent bactericidal activity of this drug. As for variations in the concentration of the drug in blood during treatment, it is advisable to attain a high peak level of short duration and a possibly low or undetectable trough level once daily (or once every other day). The higher the peak of the serum aminoglycoside concentration, the greater the antibacterial efficacy will be and the larger the area under the serum time-concentration curve (AUC) will be. The greater the AUC, the greater the accumulation of the drug in the body and the more severe the adverse effects of these drugs may be. Therefore, keeping the trough level in serum as low as possible, even undetectable, is crucial, because this translates into a reduced AUC (6, 10, 14). Due to marked accumulation of the drug, the AUC tends to be large in hemodialysis (HD) patients.

Our aim was to obtain the highest possible peak concentration and thereby reduce the AUC (to minimize systemic accumulation of the drug) by administering the aminoglycoside just before HD, based on the fact that aminoglycosides are well dialyzed because they are readily soluble in water, have a molecular mass of 700 Da or less, and show a low level of protein binding.

MATERIALS AND METHODS

The subjects in the study were 10 patients (5 men and 5 women) with chronic renal failure whose ages ranged from 49 to 79 years (mean, 69 ± 8 years) and whose dry weights ranged from 35 to 57 kg (mean, 44 ± 7 kg). Dry weight is an important concept in HD treatment and is defined as the weight at which the patient is normotensive and free of edema and is the target goal that determines the amount of fluid to be removed during the dialysis session (4). In this study, patients with massive fluid retention or sepsis were excluded. All patients were anuric, were undergoing HD three times a week, and had developed bronchitis and/or pneumonia as the first or second complication in the course of treatment.

Methicillin-resistant Staphylococcus aureus (MRSA) was isolated from sputum specimens from all 10 patients (Table 1). Written informed consent was obtained from all patients or from their closest relatives, and the study protocol was approved by the Ethical Committee of Hidaka Hospital. Arbekacin (ABK) [1-N-(34-amino-2-hydroxybutyryl dibekacin] is a new semisynthetic aminoglycoside obtained by acylation of dibekacin (11), which is readily soluble in water, has a molecular mass of 552,624 Da, and shows a low protein-bound ratio (3 to 12%). In patients with normal renal function, the half-life (t1/2) of ABK is 2.1 h and the volume of distribution (V) is 0.25 to 0.38 liters/kg (5).

ABK is effective against both gram-positive and gram-negative bacteria, as well as against almost all MRSA isolates (2, 8, 9). In Japan, the maximal approved dosage of ABK for an adult patient is 200 mg per day, which corresponds to 4 mg/kg of body weight.

Administration of ABK and HD prescription. All 10 patients were administered ABK just before HD six times in 2 weeks. Because the elimination rate of ABK during HD was an unknown factor, we aimed for a peak level of 6 to 10 μg/ml and the lowest trough level that could possibly be attained, as suggested by previous reports on HD patients receiving other aminoglycosides (3, 7). Consequently, the dose of ABK chosen was 2 mg per kg of body weight (dry weight) on the basis of the data of Fillastre et al. (5) (V = 0.32 liters/kg).

ABK sulfate was dissolved in 100 ml of saline and was administered by means of an infusion pump within exactly 60 min; the amount remaining in the infusion line was measured to calculate the actual dose.

We did not change the basic dialysis regimen prescribed for each patient; i.e., the dialyzer, blood flow rate (QB), ultrafiltration rate, the amount of dialysate delivered by a single pass of the system at a flow rate of 500 ml/min, and the time per session (4 h) were the same as usual. Three types of membrane materials, all of which were high-flux and/or high-efficiency dialyzers, were used, namely, polymethylmethacrylate (PMMA; BK80U and BK1.2U; Toray Industries Inc., Tokyo, Japan), cellulose triacetate (CTA; FB70U, FB90U, and FB130U; Nissho
Corporation, Osaka, Japan), and ethylene vinyl alcohol (EVAL; KF201C800 and KF201C120; Kawasaki Laboratories Inc., Tokyo, Japan) (Table 2). Sputum specimens were examined for MRSA once a week from the beginning of treatment for 6 weeks.

Pharmacokinetic studies. The pharmacokinetic parameters of ABK during HD were determined at the time of the first dialysis session for all patients. The pharmacokinetic parameters of ABK while the patients were not on HD were determined before the start of this study on interdialysis days 2 weeks before the start of treatment with ABK for five patients (patients 1, 3, 4, 8, and 10) who were administered the same dose used in the study of pharmacokinetic parameters during HD. One patient (patient 6) agreed to monitoring of the drug concentration in serum throughout the course of treatment.

Collection of samples. At the time of the first dialysis session, blood samples were drawn at the beginning of drug administration (time, −1 h) and at the end of drug administration, when dialysis began (time zero). At 3 to 5 min after the start of dialysis, samples were drawn from the arterial and venous ends of the dialyzer; thereafter, samples were drawn at 1, 2, 3, and 4 h. During this process, the hematocrit was also determined each time by using the blood sample from the arterial end of the dialyzer.

On interdialysis days, that is, between two sessions, with a 72-h interval from session to session, blood samples were drawn before drug administration and then at 30 min and 1, 2, 3, 4, 8, 12, 24, 48, and 72 h after the beginning of the infusion. In the patient in whom the levels of the drug in plasma were being monitored throughout the course of treatment, samples were drawn at the beginning of each dosing, at the end of dosing, and at the end of the dialysis session from the second until the last dialysis sessions. Sera were separated by centrifugation and were stored at −20°C until they were assayed.

Determination of serum ABK concentrations. The serum ABK concentration was determined by high-performance liquid chromatography (HPLC) with an LC-10A system analyzer (Shimadzu, Kyoto Japan) and an Inertsil ODS-2.5 μ column (4.6 by 150 mm; GL Science, Osaka) by the postlabeling method. The coefficient of variation for HPLC in the determination of ABK levels in human serum were found to be 2.7 to 3.8%. The limit of sensitivity of HPLC with serum was 0.2 μg/ml. A good linear relationship was found between HPLC and the coefficient of variation in serum throughout the course of treatment. Determination of serum ABK concentrations. The serum ABK concentration was determined by high-performance liquid chromatography (HPLC) with an LC-10A system analyzer (Shimadzu, Kyoto Japan) and an Inertsil ODS-2.5 μ column (4.6 by 150 mm; GL Science, Osaka) by the postlabeling method. The coefficient of variation for HPLC in the determination of ABK levels in human serum were found to be 2.7 to 3.8%. The limit of sensitivity of HPLC with serum was 0.2 μg/ml. A good linear relationship was found between HPLC and the coefficient of variation in serum throughout the course of treatment. Determination of serum ABK concentrations. The serum ABK concentration was determined by high-performance liquid chromatography (HPLC) with an LC-10A system analyzer (Shimadzu, Kyoto Japan) and an Inertsil ODS-2.5 μ column (4.6 by 150 mm; GL Science, Osaka) by the postlabeling method. The coefficient of variation for HPLC in the determination of ABK levels in human serum were found to be 2.7 to 3.8%. The limit of sensitivity of HPLC with serum was 0.2 μg/ml. A good linear relationship was found between HPLC and the coefficient of variation in serum throughout the course of treatment. Determination of serum ABK concentrations. The serum ABK concentration was determined by high-performance liquid chromatography (HPLC) with an LC-10A system analyzer (Shimadzu, Kyoto Japan) and an Inertsil ODS-2.5 μ column (4.6 by 150 mm; GL Science, Osaka) by the postlabeling method. The coefficient of variation for HPLC in the determination of ABK levels in human serum were found to be 2.7 to 3.8%. The limit of sensitivity of HPLC with serum was 0.2 μg/ml. A good linear relationship was found between HPLC and the coefficient of variation in serum throughout the course of treatment.

None of the antibiotic agents coadministered to our patients was labeled; therefore, none of them interfered with the determination of serum ABK concentrations (Table 1).

The pharmacokinetic analysis was described by the standard one-compartment model. The parameters theoretical peak serum level of the drug in serum (Cmax), elimination rate constant (Kd), apparent V, and total body clearance (CL) while on HD were calculated by the semilogarithmic plot method and the least-squares regression technique. AUC was calculated by the trapezoidal method (in simulation) and in continuous monitoring. The clearance of ABK from the dialyzer was calculated by the standard blood side determination formula: ABK clearance of the dialyzer = [A(ABK) − V(ABK)/A(ABK)] × OB (1− Hct × 1/100), where A(ABK) and V(ABK) are the concentrations of ABK at the inlet and outlet, respectively; OB is the blood flow rate of the blood pump; and Hct is the hematocrit reading (in percent) obtained at the outlet of the dialyzer. In order to assess the clearance of the dialyzers by the same standards, the overall mass transfer coefficient (Kd), which represents the efficacy of solute transport by diffusion and which is specific to the membrane material, was calculated by a simulation analysis for each of the three types of dialyzer membrane materials (12, 13) (see the Appendix).

Simulations. By using the mean values of V, Kd, and Kd obtained in the process described above, the patterns of variations in the serum ABK level when the drug is administered either just before the HD session or after the HD session was simulated. An ABK treatment schedule for HD patients who receive HD thrice a week, wherein each parameter described above was assumed to be constant and the targeting AUC method of Begg et al. (3) was taken into consideration.

RESULTS

In five patients (patients 1, 2, 6, 7, and 8) sputum cultures became negative within the second week of treatment and remained negative during the follow-up period. In patients 4, 9, and 10, a second course of treatment at a dose of 3 mg/kg was attempted, wherein the cultures of sputum from one patient (patient 9) became negative in the second week of treatment, but one patient (patient 4) died of aspiration pneumonia and another patient (patient 10) died due to sepsis; bacterial eradication could not be determined in these patients. In pa-

### TABLE 1. Background, treatment, and outcomes for all patients who participated in this study

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Body w. (kg)</th>
<th>Underlying disease</th>
<th>Complications</th>
<th>Other antibiotic(s)</th>
<th>Bacterial eradication</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>73</td>
<td>55</td>
<td>Nephrosclerosis</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethoxazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>75</td>
<td>40</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>49</td>
<td>45</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>68</td>
<td>40</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>79</td>
<td>38</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>65</td>
<td>46</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>73</td>
<td>45</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>63</td>
<td>48</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>65</td>
<td>47</td>
<td>Diabetic nephropathy</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>73</td>
<td>44</td>
<td>Nephrosclerosis</td>
<td>Acute cholecystitis pneumonia</td>
<td>Piperacillin, sulfamethazole trimethoprim</td>
<td>Alive</td>
<td>Successful</td>
</tr>
</tbody>
</table>

* M: male, F: female. Corresponds to dry weight (see text).
Patient 5, the drug was changed from ABK to vancomycin (10 mg/kg thrice weekly) with concomitant use of fosfomycin (10 mg/kg thrice weekly); however, the patient died of aspiration pneumonia in the third week of treatment and bacterial eradication could not be accurately assessed. Another patient (patient 3) died of a second acute myocardial infarction during treatment with ABK (Table 1).

The values of the pharmacokinetic parameters and the CL of ABK by the dialyzers are given in Table 2. For the dosage actually given (mean, $1.8 \pm 0.17$ mg/kg; range, 1.47 to 1.96 mg/kg), the value of each parameter was averaged, as follows: $C_{\text{max}}$, 5.8 ± 0.7 μg/ml; $K_d$, 0.28 ± 0.07 h⁻¹; $K_i$, 0.017 ± 0.003 h⁻¹; $t_{1/2}$ on HD, 2.6 ± 0.6 h; $t_{1/2}$ off HD, 42 ± 8 h; $V$, 0.31 ± 0.04 liters/kg; CL while on HD, 63 ± 17 ml/min; and CL of ABK by the dialyzer, 52 ± 15 ml/min. The CL of ABK by the dialyzer tended to be dependent on the blood flow rate and the surface area of the dialyzer. Of the three types of dialyzers used, those that used a CTA membrane appeared to be the most effective, with a $K_o$ that was greater than the $K_o$ for PMMA and the $K_o$ for EVAL. $p < 0.01$ (Student’s $t$ test); n.s., not significant.

**FIG. 1.** The $K_o$ for each of the three types of dialyzer membrane materials calculated as follows: for PMMA, $9.3 \times 10^{-3} \pm 0.96 \times 10^{-3}$ cm/min (range, $8.3 \times 10^{-3}$ to $1.1 \times 10^{-2}$ cm/min; $n = 8$); for CTA, $1.6 \times 10^{-2} \pm 0.33 \times 10^{-2}$ cm/min (range, $9.4 \times 10^{-3}$ to $2.2 \times 10^{-2}$ cm/min; $n = 22$); for EVAL, $9.7 \times 10^{-3} \pm 2.2 \times 10^{-3}$ cm/min (range, $6.8 \times 10^{-3}$ to $1.8 \times 10^{-2}$ cm/min; $n = 18$). The $K_o$ for CTA was greater than the $K_o$ for PMMA and the $K_o$ for EVAL, $p < 0.01$ (Student’s $t$ test); n.s., not significant.

**FIG. 2.** Patterns of variation in serum ABK concentrations when administered according to two different modalities, modality I (——) and modality II (–––; conventional modality). The pharmacokinetic parameters used here are the mean values given in Table 2.

**TABLE 2. Dialysis prescription and pharmacokinetic data**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Dialyzer</th>
<th>QB (ml/min)</th>
<th>Water removed (kg)</th>
<th>Dose per kg&lt;sup&gt;a&lt;/sup&gt;</th>
<th>$C_{\text{max}}$ (μg/ml)</th>
<th>$K_d$ (h⁻¹)</th>
<th>$K_i$ (h⁻¹)</th>
<th>$t_{1/2}$ (h)</th>
<th>$V$ (liter/kg)</th>
<th>CL on HD (ml/min)</th>
<th>CL of ABK by dialyzer (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMMA</td>
<td>1.2</td>
<td>160</td>
<td>0.5</td>
<td>1.47</td>
<td>5.1</td>
<td>0.30</td>
<td>0.015</td>
<td>2.3</td>
<td>47</td>
<td>0.29</td>
</tr>
<tr>
<td>2</td>
<td>PMMA</td>
<td>0.8</td>
<td>150</td>
<td>1.7</td>
<td>1.92</td>
<td>5.2</td>
<td>0.24</td>
<td>0.015</td>
<td>2.9</td>
<td>37</td>
<td>0.37</td>
</tr>
<tr>
<td>3</td>
<td>CTA</td>
<td>0.9</td>
<td>130</td>
<td>2.2</td>
<td>1.60</td>
<td>5.3</td>
<td>0.32</td>
<td>0.020</td>
<td>2.2</td>
<td>34</td>
<td>0.30</td>
</tr>
<tr>
<td>4</td>
<td>CTA</td>
<td>0.9</td>
<td>150</td>
<td>1.0</td>
<td>1.85</td>
<td>6.4</td>
<td>0.42</td>
<td>0.014</td>
<td>1.7</td>
<td>51</td>
<td>0.29</td>
</tr>
<tr>
<td>5</td>
<td>CTA</td>
<td>0.7</td>
<td>100</td>
<td>2.0</td>
<td>1.96</td>
<td>5.2</td>
<td>0.23</td>
<td>0.014</td>
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<td>0.38</td>
</tr>
<tr>
<td>6</td>
<td>CTA</td>
<td>1.3</td>
<td>150</td>
<td>3.2</td>
<td>1.64</td>
<td>5.8</td>
<td>0.35</td>
<td>0.014</td>
<td>2.0</td>
<td>28</td>
<td>0.28</td>
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<tr>
<td>7</td>
<td>EVAL</td>
<td>1.2</td>
<td>185</td>
<td>3.0</td>
<td>1.91</td>
<td>6.2</td>
<td>0.26</td>
<td>0.014</td>
<td>2.7</td>
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<td>0.31</td>
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<tr>
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<td>EVAL</td>
<td>0.8</td>
<td>120</td>
<td>1.6</td>
<td>1.80</td>
<td>5.5</td>
<td>0.23</td>
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<td>3.0</td>
<td>34</td>
<td>0.32</td>
</tr>
<tr>
<td>9</td>
<td>EVAL</td>
<td>0.8</td>
<td>155</td>
<td>0.3</td>
<td>1.92</td>
<td>7.4</td>
<td>0.22</td>
<td>0.016</td>
<td>3.5</td>
<td>43</td>
<td>0.32</td>
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<tr>
<td>10</td>
<td>EVAL</td>
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<td>1.2</td>
<td>1.96</td>
<td>6.0</td>
<td>0.20</td>
<td>0.016</td>
<td>3.5</td>
<td>43</td>
<td>0.32</td>
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<td></td>
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<td>5.8</td>
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<td>0.017</td>
<td>2.6</td>
<td>42</td>
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<td>SD</td>
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<td></td>
<td></td>
<td>0.17</td>
<td>0.7</td>
<td>0.07</td>
<td>0.003</td>
<td>0.6</td>
<td>8</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<sup>a</sup> Refers to dry weight.
best (Table 2). The $K_a$ of CTA was the highest among the three types of dialyzers (CTA > PMMA, EVAL; $P < 0.01$) (Fig. 1). In the simulation of single dosing by converting the given dose to 2 mg/kg, the patterns of variations in the serum ABK level after administration according to two modalities were drawn as semilogarithmic graphs: modality I was when ABK was administered just before HD session, and modality II was when ABK was administered just after the HD session (the conventional modality for HD patients) (Fig. 2).

The value for each parameter was calculated, and the values were as follows: $C_{\text{max}}$, 6.6 $\mu$g/ml; trough level, 1.1 $\mu$g/ml (at 48 h) or 0.7 $\mu$g/ml (at 72 h); AUC, 86 $\mu$g · h/ml (at 48 h) or 107 $\mu$g · h/ml (at 72 h). Thus, the AUC in the case of modality I was 40% of that of the AUC by the conventional modality, modality II, which was calculated to be 213 $\mu$g · h/ml (at 48 h) or 272 $\mu$g · h/ml (at 72 h).

In clinical practice, when ABK is administered to HD patients three times a week, accumulation of drug occurs after the initial dosing; therefore, the value of each parameter becomes higher after the subsequent dosings. When drug is administered, for example, for 4 weeks, the values of the pharmacokinetic parameters after the second administration were estimated to be as follows: peak levels, mean, 11.8 ± 1.1 $\mu$g/ml (range, 8.9 to 13.1 $\mu$g/ml); trough levels at 47 h, mean 1.8 ± 0.2 $\mu$g/ml (range, 1.4 to 2.1 $\mu$g/ml); trough levels at 71 h, mean, 1.3 ± 0.1 $\mu$g/ml (range, 1.1 to 1.4 $\mu$g/ml); AUC over 0 to 47 h, mean, 151 ± 13 $\mu$g · h/ml (range, 117 to 165 $\mu$g · h/ml); AUC over 0 to 71 h, mean, 207 ± 16 $\mu$g · h/ml (range, 165 to 216) $\mu$g · h/ml. The AUCs in case of modality II were estimated to be 370 ± 31 $\mu$g · h/ml (range, 288 to 404 $\mu$g · h/ml) at 47 h and 524 ± 39 $\mu$g · h/ml (range 417 to 545 $\mu$g · h/ml) at 71 h. The ratios of the AUCs in modality I/AUCs in modality II were constantly about 40% (Table 3). For the continuously monitored patient, patient 6, the peak and trough levels and AUCs yielded almost the same results (Fig. 3).

The results obtained in this study and our simulation model

**TABLE 3. Simulations of the variations (predictable range) of $C_{\text{max}}$, trough level, and AUC when ABK is administered either just before the HD session (modality I) or after the HD session (modality II)**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>$C_{\text{max}}$ range (µg/ml)</th>
<th>Trough level range (µg/ml)</th>
<th>AUC range (µg · h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48 h</td>
<td>72 h</td>
<td>Modality I</td>
</tr>
<tr>
<td>2a</td>
<td>8.9–13.1 (6.6)</td>
<td>1.4–2.1 (1.1)</td>
<td>1.1–1.4 (0.7)</td>
</tr>
<tr>
<td>4, 2, 4c</td>
<td>11.2–20.4</td>
<td>1.8–2.2</td>
<td>1.4–2.2</td>
</tr>
</tbody>
</table>

* Duration of treatment, 4 weeks.

* 2 mg/kg was given every time. Values in parentheses correspond to the values obtained after single (initial) dosing.

* The values 4, 2, 4 mg/kg correspond to giving 4 mg/kg initially and before the HD sessions when there is a 3-day (68 h in reality) interval from HD session to HD session and giving 2 mg/kg before the other sessions.

**DISCUSSION**

The results of treatment were not excellent since MRSA disappeared from only 50% of the patients (55% when the one patient who dropped out is considered). The relatively low disappearance rate might be due in part to a dosing interval that was too long and the use of an antibiotic dose that was probably insufficient.

It may be not practical to reduce the interval between HD sessions by increasing the number of dialysis sessions to more than three times a week for the sake of administering aminoglycosides more frequently, however, it is strongly suggested that a much higher dose be administered to HD patients, because the AUC in the simulation model was calculated to be 40% of that from the conventional post-HD dosing modality. Our concept involves maximizing the use of HD to control the concentration of aminoglycosides in plasma, thereby attaining high peak levels of short duration and low trough levels, like those observed with the once-daily regimen for patients with creatinine clearances of >20 ml/min (3, 6).

The values of the parameters in this simulation were estimated to be as follows: peak levels, mean, 15.0 ± 3.2 $\mu$g/ml (range, 11.2 to 20.4 $\mu$g/ml); trough levels at 47 h, mean, 2.1 ± 0.1 $\mu$g/ml (range, 1.8 to 2.2 $\mu$g/ml); trough levels at 71 h, mean, 2.0 ± 0.4 $\mu$g/ml (range, 1.4 to 2.2 $\mu$g/ml); AUC at 47 h, mean, 174 ± 12.1 $\mu$g · h/ml (range, 148 to 183 $\mu$g · h/ml); AUC at 71 h 301 ± 58 $\mu$g · h/ml (range, 214 to 334 $\mu$g · h/ml). In the case of modality II, the AUCs become extremely large when drug was administered as doses of 4, 2, and 4 mg/kg as well as 2 mg/kg.
are attributable to improved dialyzers, i.e., high-performance dialyzers. Fillastre et al. (5) reported in 1987 that the $t_{1/2}$ of ABK in serum while patients are on HD was 4.71 h (elimination rate constant, 0.147 h$^{-1}$). Agarwal and Toto (1) observed that TAF 175 L (a high-efficiency cuprammonium rayon dialyzer) was almost twice as efficient as CD 135 (a conventional saponified cellulose ester dialyzer) at removing gentamicin; the elimination rate constant was 0.263 h$^{-1}$ for TAF 175 L and 0.132 h$^{-1}$ for CD 135.

The aminoglycosides currently available on the market resemble ABK in their pharmacological properties. Our administration modality with high-performance dialyzers will offer several possible future applications for HD patients with the potential for improved efficacy and safety.

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APPENDIX

Estimation of $K_s$. Solute and fluid transport occurs during a hemodialysis session. When a high-performance dialyzer is used, these factors are expressed, as shown in Fig. A1.

When blood passes through a single hollow fiber, solute volume ($Q_b$) and solute concentration ($C_b$) change from $Q_{b0}$ and $C_{b0}$ at the inlet to $Q_{bL}$ and $C_{bL}$ at the outlet, respectively, of the hollow fiber. Likewise, on the dialysate side, water volume ($Q_D$) and solute concentration on the dialysate side ($C_D$) change from $Q_{D0}$ and $C_{D0}$ to $Q_{D0}$ and $C_{DF}$, respectively. Solute transfers across the dialysis membrane by diffusion and bulk flow. The solute transfer rate per unit of longitudinal distance of the dialyzer $\Delta z$ can be expressed as the combination of mass transfer by diffusion, $K_s \cdot A \cdot (C_b(z) - C_D(z))$, and mass transfer by bulk flow, $SC \cdot Q_D'.A' \cdot C_D(z) \cdot \Delta z$, which are expressed by the following ordinary differential equations:

$$\frac{d[C_D(z) - C_b(z)]}{dz} = -\frac{K_s \cdot A \cdot [C_b(z) - C_D(z)]}{SC \cdot Q_D'} \cdot dz \quad (A1)$$

$$\frac{d[C_D(z)]}{dz} = -\frac{Q_D}{Q_D'} \cdot A$$

For boundary conditions (BC):

for $z = 0$, $C_b(z) = C_{b0}$, $C_D(z) = C_{D0}$ and  

$$Q_D(z) = Q_{D0}$$

for $z = L$, $C_b(z) = C_{bL}$, $C_D(z) = C_{DL}$ and

$$Q_D(z) = Q_{D0}$$

in which the variable and constants are the distance from the dialyzer inlet ($z$), overall mass transfer coefficient ($K_s$), ultrafiltration rate per unit of membrane area ($Q_D'$), membrane area per unit longitudinal distance ($A'$), and sieving coefficient ($SC$; which is equal to $C_D(z)/C_b(z)$).

In the equations described above, the $K_s$ (in centimeters per minute) represents the efficacy of solute transport by diffusion which is specific to the membrane material.

Simulation analysis. Because we cannot solve the equations above analytically, they are calculated numerically as a two-point boundary problem by the Runge-Kutta method (for $z = 0$, $C_b = C_{b0}$; for $z = L$, $C_b = C_{bL}$). If we substitute the appropriate values, such as $Q_{D0}$, $Q_{DF}$, ultrafiltration rate, the entire length of dialyzer, and the membrane surface area, which are obtained from individual patients, into equations A1 and A2, the unknown parameter, $K_s$, can be determined precisely from a simulation analysis on a computer. That is, the input of the postulated value for $K_s$ into the equations is adjusted by an iterative procedure until the best fit for the clinical data is found.

REFERENCES


