NOTES
Pharmacokinetics and Dosage Requirements of Netilmicin in Cystic Fibrosis Patients

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The pharmacokinetics of netilmicin were determined in 10 patients with cystic fibrosis. Mean (± standard error of the mean) values for total body clearance and volume of distribution were 2.62 (±0.18) ml/min per kg of body weight and 0.38 (±0.01) liter/kg, respectively, and were considerably larger than the same parameters reported for patients without cystic fibrosis.

Netilmicin, the aminoglycoside antibiotic most recently marketed in the United States, has a spectrum of antibacterial action similar to that of other aminoglycosides (4, 6). Due to its activity against Pseudomonas aeruginosa, a common pathogen in the pneumonia of cystic fibrosis (CF) (11), netilmicin has potential application in this setting. It has been demonstrated by a number of investigators that the pharmacokinetics of aminoglycosides in CF patients differ from those in other populations (8, 9, 19). In view of these findings, the well-known narrow therapeutic index of aminoglycosides, and the apparent need for high aminoglycoside concentrations in the sera of patients with gram-negative pneumonia (14, 15), it is of considerable importance to evaluate the pharmacokinetics or dose-concentration relationship of any new aminoglycoside in the CF population. Michalsen and Bergan described the pharmacokinetics of netilmicin in eight CF patients (13). They found that the pharmacokinetics in the CF patients did not differ enough from those in non-CF controls to require a different dosage regimen. This finding and conclusion are in contrast to those of other investigators describing the pharmacokinetics and dosage requirements of other aminoglycosides in CF patients. It was the purpose of this study to further evaluate the pharmacokinetics of netilmicin in CF patients.

The study was approved by the Institutional Review Board before initiation, and written informed consent was obtained from all patients over 18 years of age or the parents of patients under 18 years of age. Additionally, written informed assent was obtained from patients aged 12 to 18 years.

Ten patients admitted to the hospital for treatment of an acute pulmonary exacerbation of their disease were enrolled in the study. Characteristics of the patients are presented in Table 1. Exclusion criteria included the presence of an infecting organism resistant to netilmicin, renal or hepatic impairment, a history of hypersensitivity to aminoglycosides, and pregnancy. Therapy with an extended-spectrum penicillin and netilmicin (2 mg/kg of body weight every 8 h infused intravenously over 30 min) was initiated upon admission. Blood samples were obtained at approximately 0.5, 3, and 7 h after the end of the initial netilmicin infusion and analyzed for netilmicin concentration within 24 h. The length of the drug infusion and times of blood sample collection were recorded. These data were used to individualize dosage according to the Sawchuk-Zaske (17) dosing method by using a TI-59 programmable calculator and PC-100 printer (Texas Instruments, Dallas, Tex.) to achieve therapeutic, nontoxic peak and trough concentrations of netilmicin in the serum. At least 24 h after this new dosage was initiated, blood samples were obtained immediately before and 0.5 h after a netilmicin infusion and analyzed for netilmicin concentration to assess the appropriateness of the new dose. If necessary, further dosage adjustments were made.

A blood sample was obtained immediately before administration of the last dose of netilmicin and at 10, 20, 30, and 40 min and 1, 2, 6, 10, and 12 h after completion of the drug infusion. Again, the length of the infusion and times of blood collection were recorded. Within 30 min of collection, the blood samples were centrifuged, and the serum was frozen at −40°C until it was analyzed for netilmicin concentration.

Concentrations of netilmicin in the serum were determined by using the TDx fluorescence polarization immunoassay (Abbott Laboratories, North Chicago, Ill.). The lower limit of sensitivity of the assay was 0.4 µg/ml, and the intrarun and interrun coefficients of variation were 4 and 6%, respectively.

Concentrations in serum observed immediately before and after the last dose of netilmicin in the course of therapy were analyzed to determine pharmacokinetic parameters. The terminal disposition rate constant, half-life, apparent volume of distribution at steady state, and total body clearance were determined for each patient. The terminal disposition rate and half-life (β and t1/2β, respectively) were determined from the best-fit line of the natural logarithms of concentrations in serum versus time for those points after the distribution phase, determined by least-squares regression. The slope of this line is β, and t1/2β equals 0.693 divided by β. The apparent volume of distribution at steady state (Vss) and total body clearance (CLr) were determined by noncompartmental analysis, corrected for infusion time (5). Areas under the concentration-time curve and the first-moment curve were determined by using the correction of Bauer and

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Gibaldi to account for the presence of netilmicin in serum before the last dose (1).

Calculated pharmacokinetic parameters for each patient and mean (± standard error of the mean) values are presented in Table 1. The disposition of netilmicin was characterized by a biexponential decline in concentrations in serum. A representative plot of concentration versus time (patient 1) is presented in Fig. 1. Mean (± standard error of the mean) values were $\beta = 0.381 (±0.019)$ h$^{-1}$, $t_{1/2\beta} = 1.87 (±0.10)$ h, $V_m = 0.38 (±0.01)$ liter/kg of body weight, and $CL_T = 2.62 (±0.18$ ml/min per kg).

The altered disposition of aminoglycosides in CF patients has been described by numerous investigators. Likewise, we demonstrated that the pharmacokinetic characteristics of netilmicin differ considerably from those reported in non-CF populations. The mean $CL_T$ for netilmicin in non-CF patients is 1.42 ml/min per kg of body weight (7, 16), whereas we determined it to be 2.62 ml/min per kg in our study population of CF patients. Further, $V_m$ determined in this study was 0.38 liter/kg as opposed to 0.25 liter/kg reported for non-CF patients. These differences are similar to other reports of aminoglycoside pharmacokinetics in CF patients cited previously in this paper. This also explains why our patients, on average, required a total daily netilmicin dose of 11.72 mg/kg. At the same time, it should be noted that the range of doses needed to achieve desired peak concentrations in the sera of our patients was 7.42 to 17.02 mg/kg of body weight per day. It may therefore be concluded that some CF patients do require larger than normal doses of netilmicin on a weight basis but that concentrations in the serum should be determined for each patient so that doses can be individualized.

Our findings and conclusions differ from those of Michelsen and Bergan, who do not recommend different netilmicin doses in CF patients (13). A possible explanation for this discrepancy is the fact that our study population was composed of patients undergoing acute respiratory exacerbations of their disease. It is not clear in the report of Michelsen and Bergan whether the patients fell into this category. It has been suggested that marked alterations in pharmacokinetic disposition of aminoglycosides in CF patients is related to the severity of pulmonary disease (12). Although this may explain the different findings in these two studies, it is not clear why such a phenomenon should occur. It has been speculated that perhaps extrarenal pathways of aminoglycoside elimination come into play in patients with advanced pulmonary disease (10). Further, it may be that disposition varies with respiratory status over a short period of time in the individual patient. It would therefore be of interest and perhaps importance to determine whether there is some correlation between aminoglycoside disposition and clinical condition. This might be possible through the use of one of the quantitative clinical rating systems such as those described by Beaudry et al. (2) or Taussig et al. (18) or the chest roentgenogram quantitative rating system of Brasfield et al. (3). The investigation of such possible relationships would be a desirable aspect of future pharmacokinetic studies in the CF population.

It seems reasonable to conclude that the pharmacokinetic disposition of netilmicin often varies from normal in CF patients such that higher doses are frequently required to achieve therapeutic peak concentrations in the serum. Further, routine monitoring of netilmicin concentrations in the sera of CF patients is recommended not only to allow appropriate dosing but to detect changing disposition as the pulmonary status of the patient changes.

**TABLE 1. Characteristics of patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Serum creatinine (mg/dl)</th>
<th>Wt (kg)</th>
<th>$\beta$ (h$^{-1}$)</th>
<th>$t_{1/2\beta}$ (h)</th>
<th>$V_m$ (liter/kg)</th>
<th>$CL_T$ (ml/min per kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>F</td>
<td>0.8</td>
<td>33.4</td>
<td>0.277</td>
<td>2.50</td>
<td>0.35</td>
<td>1.83</td>
</tr>
<tr>
<td>2</td>
<td>24</td>
<td>M</td>
<td>0.4</td>
<td>34.0</td>
<td>0.465</td>
<td>1.49</td>
<td>0.41</td>
<td>3.16</td>
</tr>
<tr>
<td>3</td>
<td>23</td>
<td>M</td>
<td>0.8</td>
<td>43.2</td>
<td>0.296</td>
<td>2.34</td>
<td>0.32</td>
<td>1.67</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>M</td>
<td>0.6</td>
<td>34.1</td>
<td>0.392</td>
<td>1.77</td>
<td>0.34</td>
<td>2.94</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>0.7</td>
<td>48.5</td>
<td>0.375</td>
<td>1.85</td>
<td>0.34</td>
<td>2.72</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>M</td>
<td>0.5</td>
<td>23.5</td>
<td>0.438</td>
<td>1.58</td>
<td>0.44</td>
<td>3.45</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>M</td>
<td>0.8</td>
<td>29.0</td>
<td>0.341</td>
<td>2.03</td>
<td>0.38</td>
<td>2.21</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>F</td>
<td>0.6</td>
<td>12.8</td>
<td>0.399</td>
<td>1.74</td>
<td>0.45</td>
<td>2.66</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>M</td>
<td>0.8</td>
<td>57.0</td>
<td>0.381</td>
<td>1.82</td>
<td>0.41</td>
<td>2.70</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>F</td>
<td>0.5</td>
<td>15.2</td>
<td>0.442</td>
<td>1.57</td>
<td>0.37</td>
<td>2.83</td>
</tr>
</tbody>
</table>

Mean (± SEM) 16 0.65 33.17 0.381 ± 0.019 1.87 ± 0.10 0.38 ± 0.014 2.62 ± 0.18

* Symbols and abbreviations: $\beta$, terminal disposition rate; $t_{1/2\beta}$, half-life; $V_m$, volume of distribution at steady state; $CL_T$, total body clearance.

**FIG. 1.** Disposition of netilmicin represented by a plot of concentration in serum versus time for patient 1.
We acknowledge the valuable assistance of Raymond E. Galinsky in the preparation of this manuscript.

LITERATURE CITED


