Optimal Sampling Times of Once Daily Gentamicin in Korean Patients with Urinary Tract Infections

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Abstract – The clinical use of once daily aminoglycoside (ODA) dosing has been increased because of the potential therapeutic advantages of this dosing regimen. To evaluate the optimal sampling times of ODA dosing method in a clinical setting, the study was prospectively conducted in a total of 28 patients with UTI. All of the patients were intravenously administered gentamicin at a dose of 7 mg/kg over 60 minutes and randomly divided into two groups. Blood was collected at 0, 2, and 6 hours in Group A and at 1, 2, and 6 hours in Group B after the end of the 1-hour infusion. The pharmacokinetic parameters (Ke, Vd, and Cmax) obtained using the 0, 6 hour levels and 2, 6 hour levels in Group A were statistically different while those of 1, 6 hour levels and 2, 6 hour levels in Group B were similar. This finding indicated that the distributional phase of ODA is completed within 1 hour following the end of the 1-hour infusion. If we are allowed to collect only two blood samples in ODA considering patients comfort and the analytical cost of drug, the first one should be drawn after 1 hour following the end of infusion to obtain adequate pharmacokinetic information.

Keywords □ once daily gentamicin, optimal sampling times, pharmacokinetic parameter

INTRODUCTION

Aminoglycoside antibiotics are widely used in hospitalized patient population owing to their spectrum of activity and unique mode of bactericidal action. Although they are highly effective, potential ototoxicity and nephrotoxicity have often limited the use of these agents. However, based on more recent data of efficacy and toxicity, a new dosage strategy for administering aminoglycoside in larger and less frequent dose has evolved, namely, extended-dosing intervals, or once-daily administration of aminoglycoside (Chuck et al., 2000; Morris et al., 1999).

The use of once daily aminoglycoside (ODA) regimen in the treatment of various infections is founded on the two distinct principles (Fantin et al., 1990; Freeman et al., 1997; Lacy et al., 1998; Moore et al., 1987; Rotschasfer et al., 1994; Zhane et al., 1994); first, optimal bactericidal activity can be achieved with these agents if the peak concentration:MIC (Cmax:MIC) ratio for the infecting organisms is maximized and second, the higher concentration of aminoglycoside is achieved, the longer duration of the post-antibiotic effect (PAE) is obtained.

Many clinical studies have examined the efficacy and toxicity related to ODA regimens (Barclay et al., 1994; Barclay et al., 1999; Bartal et al., 2003; Bates et al., 1994; Preston et al., 1995). Data from both animal models and clinical trials suggest that these regimens are not only as effective as conventional ones but also reduce the rates of ototoxicity and nephrotoxicity associated with aminoglycoside therapy.

In traditional dosing aminoglycoside, it is generally recommended that two drug concentrations should be drawn at 30 minute after an infusion and just before a next dose to calculate the pharmacokinetic parameters and adjust the dosage regimen. However, it is not yet known that this conventional sampling method can be applied in ODA.

In this study, we attempted to find out if we could apply the

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sampling times and frequencies of the traditional dosing aminoglycoside to ODA in a clinical setting.

**MATERIALS AND METHODS**

The study was prospectively conducted in the Emergency Room, Samsung Medical Center, Seoul, Korea from July 2000 to October 2001. Patients with urinary tract infections required parenteral aminoglycoside treatment were enrolled in this study. Subjects were included if they were over 18 years and had a normal level of creatinine in serum (Scr < 1.4 mg/dl). Subjects were excluded if they were pregnant or lactating women, and had a history of anaphylactic reaction to aminoglycoside, renal impairment (Scr ≥ 1.4 mg/dl), severe hepatic dysfunction, neutropenia, infective endocarditis, hearing loss or vestibular dysfunction.

Gentamicin at a dose of 7 mg/kg was intravenously administered to all of the patients over 60 minutes. To assess the pharmacokinetic parameters of once daily gentamicin, blood samples were drawn at 0, 1, 2, and 6 hours after the end of infusion. Considering the patients comfort and the analytical cost of drug, we divided them into two groups and limited the frequencies of blood sampling to 3 times at the first dose. Blood was collected at 0, 2, and 6 hours in Group A and at 1, 2, and 6 hours in Group B. Blood samples were obtained via direct venipuncture. The samples were analyzed by fluorescent polarization immunoassay using COBAS INTEGRA 800™ (Roche, Switzerland). If concentrations were greater than 10 µg/ml, they were reanalyzed with proper dilutions. Intra- and inter-day coefficients of variation were less than 5 percent.

**Pharmacokinetic analysis**

The elimination constant (Ke), volume of distribution (Vd), and maximum concentration (Cmax) were calculated by using the Sawchuck-Zaske method, based on two points in each group.

Based on the two points, each group was divided into two subgroups, A₁ (0 and 6 hour levels) and A₂ (1 and 6 hour levels) for Group A, B₁ (1 and 6 hour levels) and B₂ (2 and 6 hours levels) for Group B.

The measured concentrations were compared with the corresponding calculated ones at 0 hour in Group A and at 1 hour in Group B. The calculated concentrations were obtained using the Ke values derived from the slope with the two measured levels, 2 and 6 hours.

**Statistic analysis**

Descriptive statistics of patient demographics were analyzed. The pharmacokinetic parameters were compared by the paired t-test within intra-group and by the Mann-Whitney test between groups. For all data, the mean and ranges were calculated. A level of significance was p value less than 0.05.

**RESULTS**

**Patients**

Twenty-five women and three men were finally enrolled in this study. All of them were administered 7 mg/kg of gentamicin. Table I illustrates subject demographics. Demographic characteristics were not significantly different between the two groups.

**Pharmacokinetic analysis**

A comparison was made between the measured and the extrapolated 0- and 1-hour concentrations using the elimination rate constant. In Group A, the measured mean level (± SD) at 0 hour was 19.95 ± 4.24 µg/ml, which was much higher than the extrapolated one (14.82 ± 4.05 µg/ml). However, the measured and extrapolated 1- hour levels (10.65 ± 1.60 µg/ml vs 9.79 ± 1.91 µg/ml) in Group B were similar as shown in Table II.

Although the measured and extrapolated 0-hour levels were different, one exponential decay model was applied to calculate pharmacokinetic parameters for Group A and B (Table III).

In subgroups, A₁ and A₂, the mean values of Ke and Vd were 0.38 ± 0.09 hour⁻¹ vs 0.32 ± 0.08 hour⁻¹. 0.30 ± 0.08 L/kg vs 0.42 ± 0.12 L/kg, respectively. There were significant differ-

**Table I.** Demographics for Group A and Group B

<table>
<thead>
<tr>
<th>Description</th>
<th>Group A (n = 16)</th>
<th>Group B (n=12)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>46.46 ± 15.45</td>
<td>37.36 ± 15.68</td>
<td>0.238</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>3/13</td>
<td>0/12</td>
<td>0.146</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.63 ± 10.67</td>
<td>51.77 ± 7.64</td>
<td>0.837</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.10 ± 7.03</td>
<td>158.38 ± 6.13</td>
<td>0.423</td>
</tr>
<tr>
<td>Cr (ml/min)</td>
<td>55.78 ± 14.2</td>
<td>78.04 ± 11.41</td>
<td>0.423</td>
</tr>
</tbody>
</table>