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# 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 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 otovestibular toxicity 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:pathogen 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 enlisted 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, $A_1$ (0 and 6 hour levels) and $A_2$ (1 and 6 hour levels) for Group A. $B_1$ (1 and 6 hour levels) and $B_2$ (2 and 6 hour 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, $A_1$ and $A_2$, 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

| Description | Group A (n = 16) | Group B (n=12) | P value |
|---|---|---|---|
| Age (yrs) | 46.46 ± 15.45 | 37.36 ± 15.68 | 0.238 |
| Sex (m/f) | 3/13 | 0/12 | 0.146 |
| Weight (kg) | 53.63 ± 10.67 | 51.77 ± 7.64 | 0.837 |
| Hight (cm) | 160.10 ± 7.03 | 158.38 ± 6.13 | 0.423 |
| Ccr (ml/mln) | 55.78 ± 14.2 | 78.04 ± 11.41 | 0.423 |

**Table II.** Concentrations of Group A and Group B

| | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| Time (hour) | 0 | 2 | 6 | 1 | 2 | 6 |
| Gentamicin conc. (μg/ml) | | | | | | |
| Measured | 19.95 ± 4.24 | 7.74 ± 1.82 | 2.18 ± 1.16 | 10.65 ± 1.60 | 6.99 ± 1.65 | 1.93 ± 0.97 |
| Calculated | 14.82 ± 4.05 | | | 9.79 ± 1.91 | | |

**Table III.** Pharmacokinetic parameters in Group A and Group B

| | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | $A_1$ (0-6 hr) | $A_2$ (2-6 hr) | p value | $B_1$ (1-6 hr) | $B_2$ (2-6 hr) | p value |
| Ke ($h^{-1}$) | 0.38 ± 0.09 | 0.32 ± 0.08 | 0.05 | 0.36 ± 0.08 | 0.35 ± 0.08 | 0.59 |
| Vd (L/kg) | 0.30 ± 0.08 | 0.42 ± 0.12 | 0.005 | 0.39 ± 0.05 | 0.44 ± 0.08 | 0.07 |
| Cmax (μg/ml) | 19.95 ± 4.24* | 14.82 ± 4.05** | 0.03 | 15.27 ± 1.85** | 13.79 ± 2.47** | 0.11 |

*The measured concentration
**The calculated concentrations were obtained using the Ke values derived from the slope with the measured levels.

**Table IV.** The pharmacokinetic parameters in Group A.

| | Drug levels | | | | $A_1$ (0, 6 hour levels) | | | | $A_2$(2, 6 hour levels) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Calculated | | | | Ke | Vd | Cmax | Half-life | Ke | Vd | Cmax | Half-life |
| | 0 hour | 0 hour | 2hour | 6hour | ($hour^{-1}$) | (L/kg) | (μg/ml) | (hour) | ($hour^{-1}$) | (L/kg) | (μg/ml) | (hour) |
| 1 | 18.02 | 9.9 | 6.71 | 3.06 | 0.30 | 0.3 | 18.02 | 1.4 | 0.2 | 0.62 | 9.9 | 3.53 |
| 2 | 26.5 | 15.2 | 7.49 | 1.83 | 0.45 | 0.2 | 26.5 | 1.1 | 0.35 | 0.39 | 15.2 | 1.97 |
| 3 | 15.64 | 10.3 | 5.15 | 1.28 | 0.42 | 0.33 | 15.6 | 1.25 | 0.35 | 0.55 | 10.3 | 1.99 |
| 4 | 17.3 | 14.3 | 6.53 | 1.36 | 0.42 | 0.32 | 17.3 | 1.42 | 0.39 | 0.4 | 14.3 | 1.77 |
| 5 | 23.92 | 17.5 | 9.39 | 1.03 | 0.52 | 0.23 | 23.92 | 1.48 | 0.31 | 0.18 | 17.5 | 2.22 |
| 6 | 19.16 | 15.3 | 9.68 | 3.86 | 0.27 | 0.31 | 19.16 | 2.03 | 0.23 | 0.41 | 15.3 | 3.02 |
| 7 | 11.4 | 11 | 6.61 | 2.39 | 0.26 | 0.54 | 11.4 | 2.54 | 0.25 | 0.56 | 11 | 2.72 |
| 8 | 14.75 | 11.7 | 6.54 | 2.03 | 0.33 | 0.38 | 14.75 | 1.7 | 0.29 | 0.51 | 11.7 | 2.37 |
| 9 | 22.34 | 26.2 | 11.3 | 2.11 | 0.39 | 0.3 | 22.34 | 2.03 | 0.42 | 0.21 | 26.2 | 1.65 |
| 10 | 21.85 | 15.5 | 8.38 | 2.44 | 0.37 | 0.25 | 21.85 | 1.45 | 0.31 | 0.38 | 15.5 | 2.25 |
| 11 | 16.27 | 15.4 | 6.78 | 1.31 | 0.42 | 0.33 | 16.27 | 1.58 | 0.41 | 0.35 | 15.4 | 1.69 |
| 12 | 24.5 | 15.4 | 6.78 | 1.31 | 0.49 | 0.21 | 24.5 | 1.08 | 0.41 | 0.37 | 15.4 | 1.69 |
| 13 | 18.81 | 14.7 | 9.66 | 4.18 | 0.25 | 0.32 | 18.81 | 2.08 | 0.21 | 0.43 | 14.7 | 3.31 |
| 14 | 23.4 | 14.9 | 9.68 | 4.07 | 0.29 | 0.24 | 23.4 | 1.57 | 0.22 | 0.42 | 14.9 | 3.2 |
| 15 | 20.5 | 11.2 | 5.14 | 1.09 | 0.49 | 0.26 | 20.5 | 1 | 0.39 | 0.56 | 11.2 | 1.79 |
| 16 | 24.9 | 18.4 | 8.04 | 1.53 | 0.46 | 0.21 | 24.9 | 1.23 | 0.41 | 0.31 | 18.4 | 1.67 |
| Mean ± SD | 19.95 ± 4.24 | 14.82 ± 4.05 | 7.74 ± 1.82 | 2.18 ± 1.16 | 0.38 ± 0.09 | 0.30 ± 0.08 | 19.95 ± 4.24 | 1.56 ± 0.46 | 0.32 ± 0.08 | 0.42 ± 0.12 | 14.82 ± 4.05 | 2.3 ± 0.63 |

ences in Ke and Vd between the two subgroups ($p < 0.05$).

In subgroups, $B_1$ and $B_2$, the mean values of Ke and Vd were 0.36 ± 0.08 $hour^{-1}$ vs 0.35 ± 0.08 $hour^{-1}$, 0.39 ± 0.05 L/kg vs 0.44 ± 0.08 L/kg , respectively. No differences in all of the pharmacokinetic parameters were observed.

## DISCUSSION

Aminoglycosides are known to be the concentration-dependent antibiotics so that their bactericidal activity increases as the peak concentration is higher with a large dose in ODA. As compared with the traditional dosage regimen, the higher Cmax:MIC ratio ensures the bacterial killing of these agents from the PAE without the evidence of increased toxicity.

The pharmacokinetic behaviors of aminoglycosides are well explained by bi- or tri- exponential decay model (Wenk *et al.*, 1979; Zaske, 1992). When they are applied to the clinical practice, mono-exponential decay model is used to calculate the pharmacokinetic parameters.

A number of studies have investigated the optimal sampling time of aminoglycosides in conventional dosing method.

In conventional dosing method, two-sample (peak and

**Table V.** The pharmacokinetic parameters in Group B.

| | Drug levels | | | | $B_1$ (1, 6 hour levels) | | | | $B_2$(2, 6 hour levels) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Calculated | | | | Ke | Vd | Cmax | Half-life | Ke | Vd | Cmax | Half-life |
| | 1 hour | 1 hour | 2hour | 6hour | ($hour^{-1}$) | (L/kg) | (μg/ml) | (hour) | ($hour^{-1}$) | (L/kg) | (μg/ml) | (hour) |
| 1 | 10.2 | 8.4 | 6.52 | 2.36 | 0.29 | 0.44 | 13.67 | 2.37 | 0.25 | 0.56 | 10.84 | 2.73 |
| 2 | 10.18 | 9.3 | 6.28 | 1.33 | 0.41 | 0.38 | 15.29 | 1.70 | 0.39 | 0.43 | 13.65 | 1.79 |
| 3 | 9.31 | 9.3 | 6.85 | 2.05 | 0.30 | 0.48 | 12.60 | 2.29 | 0.3 | 0.49 | 12.52 | 2.3 |
| 4 | 11.16 | 11.1 | 7.96 | 2.08 | 0.34 | 0.38 | 15.62 | 2.06 | 0.34 | 0.37 | 15.57 | 2.07 |
| 5 | 10.32 | 9.5 | 6.09 | 1.04 | 0.46 | 0.34 | 16.33 | 1.51 | 0.44 | 0.37 | 14.74 | 1.57 |
| 6 | 9.12 | 8.1 | 4.97 | 0.71 | 0.51 | 0.36 | 15.20 | 1.36 | 0.49 | 0.41 | 13.15 | 1.42 |
| 7 | 8.52 | 7.9 | 5.33 | 1.11 | 0.41 | 0.45 | 12.81 | 1.70 | 0.39 | 0.49 | 11.68 | 1.77 |
| 8 | 9.37 | 7.2 | 4.97 | 1.14 | 0.42 | 0.40 | 14.28 | 1.64 | 0.37 | 0.57 | 10.38 | 1.88 |
| 9 | 13.98 | 14 | 10.04 | 2.69 | 0.33 | 0.31 | 19.44 | 2.10 | 0.33 | 0.31 | 19.4 | 2.1 |
| 10 | 12.24 | 10.7 | 8.74 | 3.91 | 0.23 | 0.41 | 15.38 | 3.04 | 0.2 | 0.48 | 13.07 | 3.45 |
| 11 | 10.92 | 10.3 | 7.05 | 1.55 | 0.39 | 0.36 | 16.14 | 1.77 | 0.38 | 0.39 | 15.04 | 1.83 |
| 12 | 12.5 | 11.8 | 9.07 | 3.14 | 0.28 | 0.37 | 16.48 | 2.51 | 0.27 | 0.37 | 15.42 | 2.61 |
| | 10.65 | 9.79 | 6.99 | 1.93 | 0.36 | 0.39 | 15.27 | 2.00 | 0.35 | 0.44 | 13.79 | 2.13 |
| | ± 1.60 | ± 1.91 | ± 1.65 | ± 0.97 | ± 0.08 | ± 0.05 | ± 1.85 | ± 0.48 | ± 0.08 | ± 0.08 | ± 2.47 | ± 0.57 |

trough levels) method was recommended due to the limited number of sampling, the accuracy and predictability of pharmacokinetic parameters and analytical cost.

In ODA, to decrease the monitoring frequency and to find out the optimal sampling method, Nicolau et al developed a nomogram by obtaining a single random blood sample between 6 and 14 hour after the start of an aminoglycoside infusion to help interpret the value and recommend a subsequent dosing interval (Nicolau *et al.*, 1995). However, this nomogram was based on serum concentration sampling immediately at the end of a 1-hour infusion. At this point, the drug still would have been in the distributional phase, resulting in erroneous estimations of the Cmax (Demczar *et al.*, 1997).

Paterson et al prospectively assessed 100 consecutive once daily courses of gentamicin or tobramycin. The immediate and six hour post-dose levels were taken. They compared the accuracy of pharmacokinetic information that was calculated by the two points or the one point of six hour. The two-point method gave more accurate pharmacokinetic parameters than method that relied on a single level (Paterson *et al.*, 1991). Many clinical investigators suggested that at least two serum concentrations should be measured to determine an optimal estimate of pharmacokinetic paramcters in ODA (Bartal *et al.*, 2003; Paterson *et al.*, 1999; Van Der Auwera *et al.*, 1991; Wallace *et al.*, 2002).

However, there has been considerable confusion as to when the aminoglycoside levels are monitored in ODA (Buijk *et al.*, 2002).

While some studies suggested the first serum aminoglycoside level was collected at 1 hour after initiation of drug infusion in ODA (Bartal *et al.*, 2003; Buijk *et al.*, 2002), a crossover study with 11 healthy volunteers receiving gentamicin dose of 7 and 2 mg/kg over 1 hour infusion demonstrated that the distribution half-life of the large dose was much longer than that of the small dose (mean 41.6 and 21.8 min, respectively, $p<0.05$) (Demczar *et al.*, 1997). Demczar et al concluded that distribution would be expected to be completed approximately 1.7 and 0.45 hours after the end of the 1-hour infusion, respectively, for the high- and low-dose groups. This finding suggested that the peak level should not be measured within 1 hour after end of infusion in ODA.

Aminimanizani et al conducted a study to assess the distribution patterns of once daily tobramycin in six adult patients with cystic fibrosis. Ten blood samples at 10, 20, 30, 45, 60, 90, 120, 240, 450, and 720 minutes post-dose were obtained following the single administration of the 10 mg/kg dose over 1-hour infusion. The half-life of distribution phase was 32 minutes and distribution phase would be expected to be 94% complete by 2 hours (four distribution half-lives). Therefore, they strongly recommended that use of one compartment model should require clinical peak level to be drawn 1 hour after the end of a 1-hour infusion with once-daily dosing, to ensure completion of the distribution phase.

The pharmacokinetic behaviors of ODA could be described more accurately using a two compartment model than a one compartment. However, considering the patients comfort and

the analytical cost of drug, a one-compartment model is preferred in a clinical setting.

In our study using the large gentamicin dose (7 mg/kg), significant differences were found between the measured and the calculated levels at 0 hour in Group A. As expected, the pharmacokinetic parameters obtained using the 0, 6 hour levels ($A_1$) and 2, 6 hour levels ($A_2$) were statistically different while the pharmacokinetic parameters of 1, 6 hour levels ($B_1$) and 2, 6 hour levels ($B_2$) were similar. This indicated that the distributional phase of ODA is completed within 1 hour following the end of an infusion.

If we are allowed to collect only two blood samples in ODA, the first one should be drawn after 1 hour following the end of infusion to obtain adequate pharmacokinetic information.

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