Chapter V
Discussion

Once-daily gentamicin dosage regimen are gradually accepted as the preferred gentamicin administration schedule , but there is still no well established dosing schedule and the necessary practice of monitoring concentration in serum.

This study was designed to investigate the serum drug level at 1-hr , 2-hr,6-hr, 8-hr and 24-hr from the beginning of short IV infusion along with the clinical responses of once-daily gentamicin in Thai patients , in order to determine the optimum serum sampling time and its relatively reference concentration for therapeutic monitoring, both nephrotoxicity and efficacy, by comparing the associations between nephrotoxicity and serum drug levels at different time points and comparing the associations between efficacy and serum drug levels at different time points .

1. Optimum serum sampling time of once-daily gentamicin dosage regimen and its relatively reference concentration for monitoring nephrotoxicity

Fifty patients who met the criteria in this study were included in the evaluation of nephrotoxicity. The nephrotoxicity was indicated in 8% of the patients which is closed to the 5 - 7% reported in other previous studies of once-daily dosage regimen (Prins et al.,1993 ; Prins et al.,1994) ,in which the dosing schedule was based on the dosing nomogram (Hull & Sarubbi, 1976).

The incidence of nephrotoxicity was higher than the incidence of 1.2% found in one recent study (Nicolua et al., 1995) which a fixed dose (7mg/kg) was administered to all patients , with a variable dosing interval depending on estimated

renal function. However, in that study the median duration of treatment was 3 days, as opposed to 6 days in this study. From studies , the duration of treatment was found to be a significant risk factor for nephrotoxicity. In addition , in that study nephrotoxicity was defined as an increase in the serum creatinine level during treatment only. It is well known that aminoglycosides associated nephrotoxicity may be come evident after the drug have been discontinued. In this study, all patients who experienced nephrotoxicity met the criteria after the last day of gentamicin treatment. The changes in some clinical laboratory tests for nephrotoxic evaluation confirmed this result , as shown in table 4.4A , 4.4B and 4.4C. All nephrotoxic patients had serum creatinine increased for more than or equal to 0.5 mg/dl. from the initial value after the last day of treatment : at the 10^{th} , the 14^{th} , the 17^{th} , the 20^{th} day since the starting the gentamicin treatment. The hypokalemia and hypomagnesemia (electrolyte imbalance which is clinical manifestation of aminoglycoside nephrotoxicity.) were developed in all nephrotoxic patients . However, one nephrotoxic patient could not determine to be hypokalemia and another nephrotoxic patient could not determine to be hypomagnesemia caused by the treatment since the patients had the initial values below the normal range.

The incidence of nephrotoxicity was considered along with serum gentamicin levels, the 24-hr serum gentamicin levels of less than 0.3 mg/L , 0.4 mg/L , 0.6 mg/L and 1.4 mg/L of the four nephrotoxic patients determined in this study indicated that the upper limit trough concentration of 2 mg/L and 1 mg/L usually recommended for clinical practice were both too high.The majority of the patients had trough levels at 24-hr of less than 0.3 mg/L which were too low to be detected by the normally used clinical analytical instrument , therefore the actual values could not be evaluated and the reference concentration could not be determined. For these reasons , measurement of trough concentration is not appropriate for once-daily dosing.

The optimum serum sampling time for monitoring nephrotoxicity was determined by comparing the associations between nephrotoxicity and serum gentamicin levels at different time points , as shown in table 4.8 . In this study , the 6-hr and 8-hr serum gentamicin levels were associated significantly with nephrotoxicity at P = 0.001 , while the 2-hr serum gentamicin level at p = 0.007. This result was the same as other study (Blaser et al.,1994) which suggested that serum aminoglycoside levels in patients receiving a once-daily dose may be derived from a sample obtained 8 hours after administration. Because of a strong correlation between these two time points serum gentamicin levels (R = 0.94) , we can use either one of these time points to monitor nephrotoxicity up to convenience.The percentage of patients showing nephrotoxicity with different 6-hr and 8-hr serum gentamicin levels were shown in table 4.10 and table 4.11. The 6-hr serum gentamicin levels of less than 3.0 mg/L or the 8-hr serum gentamicin levels of less than 2.0 mg/L provided a significantly lesser chance of developing nephrotoxicity. These serum gentamicin levels may be the relatively reference concentration for monitoring nephrotoxicity of once-daily gentamicin dosage regimen by obtained sample at 6 hours or 8 hours after administration. However, the number of the nephrotoxic patients in this study was still too small to make a strong confident conclusion.

Several other risk factors associated with nephrotoxicity were analyzed by univariate analysis. The long duration of treatment determined to be a significant risk factor while no significant associations between some other clinical status of patients (hypokalemia before treatment , hypomagnesemia before treatment , liver dysfunction or volume depletion) and nephrotoxicity were found. It is possible that a relatively small sample size prevented the finding of this association.

2. Optimum serum sampling time of once-daily gentamicin dosage regimen and its relatively reference concentration for monitoring efficacy

Thirty-seven documented infected patients who met the criteria of this study were included in the evaluation of efficacy. Favourable efficacy was recorded in 73% of these patients.

The optimum serum sampling time for monitoring efficacy was determined by comparing the associations between favourable efficacy and serum gentamicin levels at different time points , as shown in table 4.18. The 1-hr serum gentamicin level was associated significantly with favourable efficacy at $P< 0.05$, while the 2-hr serum gentamicin level at $p < 0.1$ .This result was the same as other investigations (Moore et al.,1984; Moore et al.,1987) which suggested that achieving adequate peak concentration associated with clinical outcome. The percentage of patients showing favourable efficacy with different 1-hr serum gentamicin levels was shown in table 4.19. The 1-hr serum gentamicin levels of more than or equal to 11.0 mg/L provided a significantly greater chance of having a favourable efficacy. This serum gentamicin level may be the relatively reference concentration for monitoring efficacy of once-daily gentamicin dosage regimen by obtained sample at 1 hour after administration.

It was possible that confounding clinical factors ,such as those in table 4.21 , might explain the association between the efficacy and the 1-hr serum gentamicin levels. However, in this study the sample size did not allow a sufficiently powerful analysis of association between several potential important factors and efficacy. For example ,the numbers of patients with infection of the lower respiratory tract , the skin , the abdomen or the urinary tract were all too small to be assured of the associations between efficacy and these infections. Similarly , the associations between efficacy and infection with organisms could not confidentially be determined.

However , lower respiratory tract infection and infection with *Pseudomonas* species appeared to be associated with an increased unfavourable efficacy of once-daily gentamicin therapy for the patients in this study. The distribution of an antimicrobial agent within the body is believed to be a critical factor in determining its therapeutic efficacy (Parry & New,1978.). The penetration of the aminoglycosides into bronchopulmonary secretions has been studies by several investigators. The results are conflicting , with relatively poor penetration found by some (Wang et al.,1975; Alexander et al.,1979) and adequate levels found by others (Dull et al., 1979; Hull et al., 1977).The activity of the aminoglycosides in bronchopulmonary secretion may depend ,in part, upon the purulence and mucoid nature of the sputum and the infecting organism. It is not known if high blood concentrations of the aminoglycosides will definitely lead to high concentrations in the pulmonary tissues and secretions. Anyway, the higher serum levels were likely at least be reflected in the highly vascular pulmonary tissues. The results in this study may be the case . There were five lower respiratory tract infection patients, four of them were evaluated in unfavourable efficacy group. Their 1-hr serum gentamicin levels were 6.1 mg/L , 8.7 mg/L , 8.9 mg/L and 10.8 mg/L while the serum of a favourable efficacy patient was 12.0 mg/L. All of the *Pseudomonas* infected patients were lower respiratory tract infection patients. Besides as previously mention, the minimum inhibitory concentration of *Pseudomonas* is higher than other organisms (median 2 mg/L ,range 0.5 - 4 mg/L) which reflect the need of higher 1-hr serum gentamicin levels.

No significant associations were found between the concurrently administered antibiotics and efficacy. Eventhough it might be expected that the use of some other antibiotics, such as cephalosporins concurrently would have led to increase efficacy. And again , a relatively small sample size might prevent the finding of this association.

3. Pharmacokinetic data

The elimination rate constant , half-life , volume of distribution and clearance of all patients were calculated , as shown in table 4.22.

The elimination rate constant of gentamicin in Thai patients was 0.26 ± 0.09 per hour while the elimination rate constant of foreign patients reported in the literature was 0.20 ± 0.09 per hour (Zaske, 1994) . The half-life of gentamicin in Thai patients was 3.04 ± 1.25 hours while the half-life of gentamicin in foreign patients was reported to be 2.2 ± 2.1 hours. The volume of distribution in Thai patients was 0.32 ± 0.08 L/kg while that reported for foreign patients was 0.19 ± 0.08 (Zaske , 1994).