CHAPTER V

CONCLUSION

For the neonate, gentamicin is described as the drug of choice for treatment of gram – negative sepsis and multiple daily regimens have been used for more than three decades.[3,87] Rapidly developing antibiotic resistance has created a need for better use of currently available agents and the development of news , more effective agents and therapeutic approaches. One of these never approaches is the administration of aminoglycosides in larger , single , daily doses.[4] Presently , the concept of once – daily dosing of aminoglycosides seem to be proliferating rapidly world wide.[88] This study was designed to investigate the serum gentamicin levels, pharmacokinetic parameters and pharmacological response after twice – daily dosing and once – daily dosing of gentamicin in Thai neonates.

Fifty – four neonates admitted at Queen Sirikit National Institute of Child Heath were included and completed the study. Twenty-seven patients in the TDD group were 14(51.85%) males and 13(48.15%) females while those 27 patients in the ODD group were 16(59.20%) males and 11(48.74%) females. There were no significant differences in characteristics of patients such as gestational age, postnatal age, weight, height, Apgar scores at 1 minute and 5 minutes between both groups ($p>0.05$). Apgar score at 5 minutes of both groups were ≥ 7. The results obtained from this study could be concluded as follow: -

1. Steady – state gentamicin peak level of the ODD group was significantly higher than the TDD group and trough level of the ODD group was significantly lower than the TDD group. Only six infants (22.22%) in the ODD group had peak level which were lower than 8 μg/ml and among these, all of them were higher than 5 μg/ml while twenty – four infants (88.89%) in the TDD group had peak level which were lower than 8 μg/ml and among these, 7 infants (25.93%) had their peak level which

were lower than 5 μg/ml. The percentage of the patients whose peak and trough levels were not within the desirable therapeutic range (peak 4-12 mg/l and trough ≤ 2mg/l) after treated with traditional dosage regimen or twice – daily dosage regimen was 11.11% (two patients with too high trough level and one patient with subtherapeutic peak level). None of the patients treated with once daily dosage regimen resulted in undesirable peak level, while there was only 3.7% (1 patient) who showed undesirable trough level (> 1.5 mg/l but less than 2 mg/l).

2. The volume of distribution (Vd) and the clearance of gentamicin (Cl) were not significant differences between the TDD group and the ODD group. The mean elimination rate constant (K) was significantly lower in the ODD group as compared to the TDD group which resulted in significantly longer elimination half life (t 1/2) in the ODD group than in the TDD group which might due in part to the less development of the kidney function of the infants in the ODD group as could be seen from the higher mean serum creatinine concentration at the first day and the third day in ODD group than the TDD group even though it was no significant difference ($p>0.05$) and the mean postnatal age was shorter in the ODD group with the p value equal to 0.150. The pharmacokinetic data varied widely in the neonates.

3. Good correlation were found between clearance of gentamicin (Cl) in l/hr and postnatal age (PA) in day, weight (Wt) in gm, serum creatinine (SCr) in mg/dl, creatinine clearance (Clcr) in ml/min/1.73m^2 or in l/hr ($r = 0.84$). Clearance of gentamicin were calculated from the serum concentrations data obtained from the blood samples collected. In clinical practice, the equation Cl (l/hr) = -0.0558 + 0.0118 PA (day) – 0.0630 SCr (mg/dl) + 7.6680 x 10^{-5} Wt (gm) was the most simplify and can be applied to predict the dosage of gentamicin for neonates using this calculated Cl and the population Vd of the neonates (0.45 ± 0.1 l/kg) when serum gentamicin concentration were not available.

4. Serum creatinine concentration of the TDD and the ODD groups before treatment with each of dosage regimen were not significantly different between groups (p>

0.05). Serum creatinine concentration at the discontinuous day of gentamicin treatment in the TDD group was significantly higher than that obtained at the third day of the same patients while no significant difference was detected in the ODD group. Relationship between the duration of gentamicin therapy and the changing in serum creatinine level at the discontinuous day from the third day of the infants in the TDD group was moderately correlated (r = 0.612) while this correlation was quite low (r = 0.105) in the ODD group. This result indicated that the serum creatinine concentration had the tendency to be increased when the duration of gentamicin therapy was increased in the patients who was given twice daily dosing regimen. There was significant increased in serum creatinine evel when using gentamicin more than eight days in the TDD group while there was no significant increase in the ODD group. In summary, treatment with ODD regimen did not present more nephrotoxicity than treatment with TDD regimen in contrary, serum creatinine concentration had more tendency to be increased after the TDD regimen than ODD regimen.

5. All patients (100%) in either the TDD group or the ODD group showed the improved outcome. The mean duration of once- daily treatment appear to be shorter than twice-daily treatment. The duration of treatment in the ODD group showed tendency to be shorter than the TDD group for most diseases with indication of gentamicin treatment such as in patients with PROM and PROM with sepsis, MAS and pneumonia. The result was indicated that once daily dosage regimen can achieve at least equivalent efficacy as compared to twice daily dosage regimen of gentamicin.

In conclusion, this study confirmed the results of those studies that once - daily dosing of intravenous aminoglycoside could achieve efficacy equivalent to traditional regimen with no increase, and possibly a decrease in toxicity.[22-33] The study showed that a 4-5 mg/kg ODD regimen of gentamicin given to neonates during the first 7 days of life produced peak concentration that may have greater clinical efficacy and trough concentration that may have less toxicity than conventional dosing regimen. By increasing the dosing interval in neonates undesired subtherapeutic peak and elevated trough concentration of more than 2 mg/l were not found. Twice daily regimen resulted in a higher percentage of

subtherapeutic peak level and elevated trough concentration of more than 2 mg/l. This reason in combination with the high variability of pharmacokinetic parameter of gentamicin in neonates make it more necessary to monitor gentamicin serum concentration when a twice daily aminoglycoside regimen is employed in neonates especially in neonates with serious infection or had tendency to use gentamicin longer than ten days as compared to the once daily regimen. In this study, since the patients with renal abnormalities or other condition that could alter gentamicin pharmacokinetic were excluded when once daily dosage regimen will be applied to such patients, caution and further studies are required before once daily gentamicin dosing can be recommended for them.

Further studies to examine whether or not the once daily dosage regimen could improve clinical outcome in proved septicemia and cost – effectiveness should be continue in neonates.