DISCUSSION

We have conducted the study to investigate the efficacy and safety of the new gentamicin regimen according to Neofax guideline in fifty Thai neonatal patients. The dose and duration of gentamicin recommend by Neofax were base on gestational ages of ≤ 29 weeks, 30-33 weeks, 34-37 weeks and ≥38 weeks and the body weights. For the prevention of bacterial infection, gentamicin was initiated on the first day of life except in neonates of group IV who received gentamicin during the first day to 8 days of life. The duration of gentamicin treatment was ranged from 1-10 days but most of the cases were withdrawn from this aminoglycoside on Day 8 after the negative result of their hemocultures had been reported. Two cases of triple twin (GA ≤ 29 weeks, weight < 0.5 gm) died during 48 hours of life after receiving the first dose of gentamicin, despite their appropriate initial gentamicin levels. The cause of death was not associated with gentamicin but might be due to hyaline membrane disease. Patent ductus arteriosus was recognized in 9 cases of neonates with GA ≤ 29 - 33 weeks. Indomethacin and ibuprofen, the NSAIDs useful for closure of the PDA were given to 8 cases and 1 case, respectively. Cenzo et al. suggested that indomethacin is associated with a lower rate of gentamicin clearance since inhibition of prostaglandin synthesis might affect renal function.[31] However, this study did not find significant difference in gentamicin levels and clearance in neonates who received indomethacin although 4 cases had slight increase in serum creatinine. The reason might be due to a short duration of indomethacin therapy (2 days). The initial standard regimen to treat suspected bacterial infection in neonatal patients is a combination of ampicillin and gentamicin. Therefore, the two drugs were given to all cases. Gentamicin was discontinued in 2 neonates and was switched to cefotaxime to cover the resistance bacteria. Premature neonates (GA ≤ 33 weeks) received more medications than term neonates, such as indomethacin and ibuprofen for closure their PDA, survanta and aminophylline to improve their pulmonary functions, calcium gluconate, ranitidine, furosemide, dopamine, metronidazole and antiretroviral; zidovudine and nevirapine.

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The drugs that might potentiate the nephrotoxicity of gentamicin were indomethacin and furosemide. However, as mention earlier, these medications were given to neonates for a short period of time and did not affect their renal function.

With regards to optimal gentamicin therapy, there is no uniformity in the current recommendation of dosing regimen of gentamicin in neonates. The development of optimized dosage schedule for neonates requires the knowledge of the relationship between gentamicin pharmacokinetic parameters and several demographic, developmental and clinical factors which might be associated with changes in gentamicin disposition. This rationale has been partly confirmed by two previous studies which demonstrates the gestational age as a good predictive value in estimating pharmacokinetic parameters especially clearance and optimum dose/day.[32] Moreover, gentamicin has its unique pharmacodynamic characteristic, the postantibiotic effects. The pattern of its bactericidal action is a concentration dependent, and its toxic effect is related to high trough concentration. Because of these, the high peak and low trough concentrations are the important factor influencing the dosing regimen of gentamicin.

The other important factor is the difference in the strength of gentamicin preparations, which composes of 80 mg/2ml and 20 mg /2 ml (not available in our University Hospital). Since the dose of gentamicin required for neonates is very small, the preparation for adult (80 mg /2ml) would result in a dilution error and therefore not recommended for use in neonate. In this study, we purchased the 10 mg /2 ml preparation to decrease the error from dilution method. In addition, the method of gentamicin administration is also important. The previous method routinely used for gentamicin administration is to start from drawing the proper dose and dilute with 5% dextrose and push into the infusion line. Thereafter the infusion rate is adjusted to approximately 30 minutes. To decrease the error regarding drug administration, we decided to use the infusion pump (syringe pump TE331 purchased from Terumo™). Meanwhile, the research nurses were informed to learn about the method of drug dilution and administration via the infusion pump. The time of administrations and the time of blood samplings were closely followed up and the actual time must be recorded in parallel with the calculated time in the case record form.

The dosage regimen of gentamicin in this study was based on the Neofax guideline by dividing the neonates into 4 groups depending on their gestational ages; GA $\leq$ 29, 30-33, 33-37

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and ≥ 38 weeks. The highest dose (5 mg/kg) and the longest dosing interval (48 hr) were recommended for neonates with GA ≤ 29 weeks. The reasons were due to their higher V_d as well as lower CL and longer $t_{1/2}$. The dose of gentamicin for neonates with GA 30-33 weeks was slightly less than the first group (4.5 mg/kg) with the same dosing interval. Neonates with GA > 34 weeks received the same dose of 4 mg/kg, however, the dosing interval was 36 and 24 hr for neonates with GA of 33-37 and ≥ 38 weeks, respectively. The rationale of this dosage guideline was based on the differences in V_d and clearance as well as the $t_{1/2}$ of gentamicin, which depended on neonatal gestational age. In addition to a lower V_d, neonates with GA ≥ 34 weeks has a higher gentamicin CL and a shorter $t_{1/2}$ thus the dose and the dosing interval of gentamicin in this study were less than those values for neonates with GA ≤ 34 weeks.

The aim of this study was to determine the efficacy and safety of Neofax guideline in 50 Thai neonates. The sample sizes of neonates in each group were ranged from 10-16, which were considered to be adequate for phase I study. The dose of gentamicin and the dosing interval of its administration were given as recommended by Neofax guideline mentioned earlier. Gentamicin concentrations were determined at 5 points; after the 1st, the 3rd and the 6th doses for evaluation of initial and maintenance therapeutic peak concentrations, respectively, before the 3rd and the 6th doses for evaluation of trough concentrations. The result showed that the initial gentamicin levels after the first dose in all groups were within the therapeutic level of 4-12 ug/ml in 47 of 48 neonates (98%). Since the efficacy of gentamicin was related to an early attainment of therapeutic peak concentration, this study supported that the first dose of 4-5 mg/kg based on GA as recommended by Neofax was appropriate. Likewise the maintenance peak concentrations at steady-state after the 3rd and 6th doses were within the therapeutic range in 38 of 40 neonates (95%) and 15 of 15 neonates (100%), respectively. The trough concentrations were also within the safety range of < 2 ug/ml in all neonates. In addition to a decrease in toxic drug accumulation, the advantage of longer duration of low gentamicin level might also prevent the rapid development of microbial resistance.[33] Thus, the result of this study showed that the maintenance dose and dosing interval as recommended by Neofax were appropriate for Thai neonates. The gentamicin pharmacokinetic parameters such as K_e, CL, V_d and $t_{1/2}$ were determined. The result showed that the mean K_e, CL and V_d were increased as gestational age increased but vice versa for the $t_{1/2}$. Statistical analysis showed that the mean values of K_e, CL

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and $t_{1/2}$ of neonates in group I (GA $\leq$ 29) were not significantly different from neonates in group II (GA 30-33 weeks). Similarly, the values of these parameters obtained from neonates in group III were not significantly different from neonate in group IV (GA $\geq$ 38 weeks). Regression analysis showed a weak correlation between GA and the parameters; K_e, CL and $t_{1/2}$, however, the values of these parameters were significantly different depended on gestational age with a cut-off point of 33 weeks. The mean K_e and CL for neonates with GA $\leq$ 29 – 33 weeks were 0.0685 hr^{-1} and 0.0355 L/kg/hr, respectively. These values increased to 0.113 hr^{-1} and 0.069 L/kg/hr in the neonates with GA 34 - $\geq$ 38 weeks and were significantly different with *P* values of 0.013 and 0.002, respectively. These findings were in line with the study by Cenzo et al. who found that gentamicin clearance increases from 0.032 to 0.037 and maximizes at 0.047 L/kg/hr for neonates with GA $\leq$ 28 weeks, GA 28-34 weeks and GA $\geq$ 34 weeks, respectively.[31] Since gentamicin is solely eliminated via the kidney, its clearance is dependent on the neonatal kidney function. Because the initial GFR is low at birth especially in premature neonates and up to postconceptional age of 34 weeks that the GFR increases rapidly.[13] Moreover, Kasik et al. revealed that the development of renal function is better correlated with postconcenptional age, therefore, influences gentamicin CL and its $t_{1/2}$.[20] The increase in gestational age increases the GFR and the CL of gentamicin thus results in a decrease in the gentamicin $t_{1/2}$. After measuring multiple linear regression, Izquierdo et al. concluded that gestational age is the most predictive variable of gentamicin CL and body weight has a good predictive value in estimating the V_d in normal term though the predictive value diminishes in preterm neonates.[32] From the present study, the mean $t_{1/2}$ of gentamicin was longest in neonates with GA $\leq$ 29 weeks (11.97 hr) then declined to 10.82 hr, 7.62 hr and 6.70 hr for neonates with GA 30-33, 34-37 and $\geq$ 38 weeks, respectively. The correlation between the GA and the $t_{1/2}$ was rather weak, however, the cut-off point for the significant difference between gestational age groups was at 33 weeks, similar to K_e and CL. The mean $t_{1/2}$ for neonates with GA $\leq$ 29- 33 weeks was 11.39 hr, while, this value for neonates with GA 34 – $\geq$ 38 weeks was 7.16 hr. Similar to the report of Cenzo et al, the median $t_{1/2}$ was 10.2 hr for neonates with GA < 28 weeks and 6.98 hr for those with GA > 34 weeks. The values of V_d in our study were not different from previous study. Our result showed that the mean V_d in Thai neonatal patients was 0.51, 0.54, 0.61 and 0.62 L/kg in group I-IV, respectively, compared to 0.5-0.7 L/kg of previous study. The V_d of neonates in group IV with GA $\geq$ 38 weeks

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was significantly greater than neonates in group I and II with GA of ≤ 29 weeks to 33 weeks. This finding was opposed to the previous study that revealed the higher V_d of gentamicin in preterm neonates when compared to term neonates. The reason was due to a greater extracellular fluid in preterm neonates. However, the significant factor might be from the low intake of IV fluid of neonatal patients. Similar to the GA, the result showed that BSA also had a weak correlation with all parameters of gentamicin. The positive correlations to BSA were associated with K_e, CL, V_d while negative correlation was found with the $t_{1/2}$. Despite a weak correlation between the GA, BW and BSA to these pharmacokinetic parameters, statistic analysis yeilded *P* values of < 0.005 confirming a significance of the apparent association between these demographic data and gentamicin pharmacokinetics. In fact a significant level is a function of both the size of the correlation coefficient and the number of observations. Because of this, a weak correlation can be statistically significant if base on an adequate number of observations, while a strong correlation may fail to achieve significant if there are only a few observations. BW correlated best to gentamicin pharmacokinetic parameters, while GA and BSA correlated fairly. Therefore BW was also considered a good predictive variable for gentamicin pharmacokinetic parameters and should be included as a factor for calculating gentamicin dosage.

The serum creatinine, BUN and trough gentamicin concentrations were used as indicators of gentamicin-induced nephrotoxicity in this study. In fact, Cenzo et al. revealed the weak correlation between creatinine clearance and pharmacokinetic parameter of gentamicin in neonates.[31] In addition Khalil and Matthews revealed that serum creatinine in preterm neonates reflects their fluid status more than their renal function.[34] The values of serum creatinine levels from all gestational age were highest in the first day of life, then decline to the normal range within 3-4 days, except neonates in group I. Since serum creatinine in the first day represents the value of creatinine level from the mother, this value could not be used as the indicator to evaluate the neonatal kidney function. Normally the creatinine level declines until reaching the true value for neonate approximately on the third day of life. In this study, the creatinine concentrations for neonates in group III and IV (GA 34- ≥ 38 weeks) declined from the highest concentrations from the first day to normal range within 3-4 days (P<0.001-0.0.038). Although the creatinine concentrations for neonates in group II had the trend to decline, their values did not reach the normal range of 0.3-0.6 mg/dl on the 3rd day of life. The creatinine concentrations for neonates in

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group I were persistently high than the normal range until the 3rd day. The reason might be due to the immaturity of their renal function or the influence of maternal creatinine therefore we could not monitor the serum creatinine until it declined to normal range. The mean BUN in all groups were within the normal value. For neonates in group I and II (GA ≤ 29 -33 weeks), the mean BUN slightly increased on the fifth day but did not reach statistical significance. According to the results from Kirsten et al. and Hayani et al., the administration of 5 mg/kg/day of aminoglycoside for 3 days or less does not lead to elevation in serum creatinine and BUN.[33,34] Similar to this study, the predictive indicators of gentamicin-induced nephrotoxicity measured by serum creatinine, BUN and gentamicin trough concentrations showed no serious effect on the renal function of neonates. Therefore, we concluded that the Neofax guideline provides low incidence of nephrotoxicity until the 3rd day of gentamicin treatment for preterm and up to the 7th day of treatment in term neonates. The interesting result from this study showed that pharmacokinetic parameters of neonates with GA ≤ 29 weeks were not difference from neonates with GA 30-33 weeks. Therefore the recommended dose of 5 mg/kg for neonates with GA ≤ 29 weeks might be decreased to the same dose of 4.5 mg/kg in neonates with GA 30-33 weeks.

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