INTRODUCTION

Neonatal bacterial infection is a common cause of morbidity and mortality, therefore, required early diagnosis and implementation of appropriate antibiotic therapy. However, individualized pharmacokinetic dosing of antibiotic therapy in neonate is necessary since the physiology such as total body water, liver function and renal function of neonates from birth to 28 days of life are altered. These factors will affect pharmacokinetic parameter and blood levels of antibiotic in neonates more than adults.

Infectious diseases such as pneumonia, endocarditis, urinary tract infection (UTI) or septicaemia in neonates are usually caused by Gram-positive bacteria especially group B streptococcus and/or Gram-negative rods such as *Escherichia. coli*, Klebsiella, Pseudomonas species and Serratia. Aminoglycoside especially gentamicin with or without another antibiotic is the most common drug prescribed since it is highly active against these pathogens and is less expensive. Moreover, it possess concentration dependent bactericidal action, post-antibiotic effect and the better understanding of risk factors associated with its use in clinical practice. Nevertheless, the use of gentamicin is limited from the reason that it requires rapid achievement of therapeutic peak serum concentration and the risk of drug toxicity; nephrotoxicity and ototoxicity related to elevated serum trough concentration. Because of these, monitoring of the peak and trough serum concentrations are mandatory for both neonates and adults.[1] The risk of gentamicin induced nephrotoxicity and ototoxicity, although controversial in neonates is considered a potential hazard related to drug accumulation. Until substantial evidence proves otherwise, maintaining serum gentamicin concentration within the accepted therapeutic range in neonates continues to be prudent.[2] Clinician should monitor clinical outcome and adverse drug reactions especially ototoxicity and nephrotoxicity in neonates. In fact it is difficult to monitor clinical outcome in neonates because they can not describe any symptom to clinician. Therefore a significant method used to follow efficacy and toxicity is monitoring blood gentamicin level to adjust the suitable dosage and dosing interval.[3]

Therapeutic effect and toxicity of gentamicin depend on blood gentamicin levels. In UTI, soft tissue infection or septicaemia, the peak gentamicin concentration should be between 4 to 8 ug/ml and trough concentration between 0.5 to 1.5 ug/ml. However in pneumonia, burn or severe infection, the peak concentration should be within 8 to 10 ug/ml and trough concentration should be kept within 1.0 to 1.5 ug/ml. Faye et al. (1999) revealed that in adult, if peak concentration higher than 5 ug/ml within 24 hr of treatment could decrease mortality and increase the rate of response of pneumonia, septicaemia, soft tissue infection and UTI.[4] While nephrotoxicity and ototoxicity will occur if prolonged trough concentration greater than 2 ug/ml.

In the past, the recommended dose of gentamicin in adult was 80 mg every 8 hr. According to this dose, the risk of drug toxicity due to accumulation of gentamicin in the kidney and the ear was increasing. In 1974, Labovitz et al. showed that single daily dose of gentamicin could reduce the risk of gentamicin toxicity. Similarly in 1994, Schumock et al. showed that higher than 27% of clinician preferred to prescribe single daily dose of gentamicin, and the number of clinician prescribing this dose of gentamicin was higher than 80% in the year 2000. There are many studies comparing the efficacy and safety between gentamicin administered once daily dose and multiple daily doses. The results show no differences in its efficacy but single daily dose can reduce drug accumulation in the kidney and the ear. The reasons describe these results are as followed;

1. Gentamicin has postantibiotic effects and the drug continues to suppress the bacterial growth despite the decline of its concentration below the minimal inhibitory concentration (MIC), which may last up to 6 hr.

2. The pattern of bactericidal action of gentamicin is concentration dependent, therefore the higher the peak/MIC ratio, the higher the killing rate. Since divided or multiple daily dosing administration results in relatively low peak/MIC ratios (<5), the same total daily dose if given as a single bolus administration will result in much higher peak/MIC ratio of >10.

3. The accumulation of gentamicin in the kidney and the inner ear is related to the trough concentrations. If the trough concentration is lower than 1.5 ug/ml or almost approched zero, the

extent and duration of accumulation of the drug will decrease. However, other factor such as age, dehydration, liver disease or concomitant use of other nephrotoxic drugs should also be accounted.[3,5]

In the past, the dosage of gentamicin given to neonates was base on gestational age, postnatal age or postconceptional age (PCA; gestational age + postnatal age) and birth weight. For example, if the gestational age is < 34 weeks and weight at birth is < 1,500 grams, the dose of gentamicin will be 3 mg/kg every 24 hr. If the weight at birth is > 1,500 grams and the gestational age is < 34 weeks, the dose of gentamicin will be 2.5 mg/kg every 18 hr. However, if the weight at birth is > 1,500 gram and the gestational age is > 34 weeks, the dose of gentamicin will be the same (2.5 mg/kg) but the dosing interval will be decreased to every 12 hr. In term neonates and postnatal age > 7 days, the dosage of gentamicin will be increased to 5 mg/kg every 12 hr.[6] Recent studies suggest that the initial dose of 2.5 mg/kg gentamicin will result in a lower blood level than therapeutic level and a higher dose, extended-interval of gentamicin will achieve therapeutic level with lower toxicity.[7]

There are few pharmacokinetic studies of gentamicin in Thai neonates. In 1995, Auruwankul studied in 32 Thai neonates at the Faculty of Medicine, Chiang Mai University, recommended the dosage of gentamicin for the Thai neonates as followed

PCA (weeks)	Weight (gm)	Gentamicin dose
< 28		4-4.5 mg/kg q 18-24 hr
28-34	< 1,500	3 mg/kg q 18 hr
	> 1,500	2.5 mg/kg q 12 hr
> 34		2.5 mg/kg q 12 hr

Kitsommart in 1998, determined the peak and trough concentrations of gentamicin after these recommended doses in 55 neonates at the same institute. The results showed that the peak concentrations of gentamicin are within the therapeutic range of 4-12 ug/ml. However, the trough concentrations in all groups are greater than 2 ug/ml indicated the risk of drug toxicity. Therefore the interval of gentamicin administration should be longer to avoid the high trough concentration.[9] In 2001, Chotigeat et al. compared a 4-5 mg/kg of gentamicin once daily versus 2-2.5 mg/kg of gentamicin twice daily in Thai neonates. Result showed that once daily dose of 4-5 mg/kg

gentamicin was an appropriate regimen in term neonates during the first 7 days of life. These regimen produced peak concentration that lead to greater clinical efficacy and trough concentration with less toxicity than conventional dosing regimen.[10]

In the Department of Pediatric, Faculty of Medicine, Chiang Mai University, the new dosage regimen of gentamicin is recently implemented following from Neofax 2002 guideline. The Neofax guideline suggests a higher dose but extended dosing interval base on gestational age. Nonetheless, the data concerning the safety and efficacy as well as gentamicin pharmacokinetics of these new regimens in Thai neonates have not yet appeared, therefore, the study is deemed necessary.

The present study was designed to investigate the efficacy, safety and pharmacokinetic parameters of gentamicin administrations in Thai neonates base on Neofax guideline. The peak and trough gentamicin levels were monitored and were used to evaluate the pharmacokinetic parameters.

LITERATURE REVIEW

The physiology of the neonate population is a very dynamic one. Alterations of body composition and physiological function of the liver and the kidney influenced pharmacokinetics and pharmacodynamics of drug occur with maturation and growth through childhood. Differences in pharmacokinetic parameters such as absorption, distribution, metabolism and elimination are due to

1. Absorption: Several age-related factors may affect the oral absorption of drugs.

1.1 Gastric pH: At birth gastric pH ranges from 6-8 due to residual amniotic fluid in the stomach (amniotic fluid is regularly swallowed during intrauterine life), gastric pH then falls to a pH of 1.5 to 3 within 24 to 48 hr after birth but during the first week of life returns to neutraLy. Gastric pH decreases gradually to adult values after approximately 2 years of ages.

1.2 Gastric emptying time in neonates and premature infants is prolonged results in delayed drug absorption. A delay in the time to peak as well as a decrease in the peak concentration of several drugs may be seen.

1.3 Pancreatic function: Concentration of amylase and lipase activity are decreased in infants < 4 months, especially in premature.

1.4 Biliary function: Bile acids are reduced to 50% of adult values in full term infants result in poor absorption of lipophilic drugs.

2. Volume of distribution (V_d) describes the relationship between the amount of drug in the body and its plasma concentration depends on.

2.1 Body compartment size such as extracellular fluid (ECF), volume compartment, intracellular fluid (ICF), lipid compartment, muscle mass, hemodynamics, plasma protein concentration, organ size and tissue perfusion. Compare to adults, total body water (TBW) and ECF are much higher in children less than a year of age and are highest in the fetus and premature neonates (Table 1). Generally, this increase in TBW results in an increased in volume of distribution of water soluble drug.

Table 1. Some factors affecting drug distribution and disposition [11]

Factor	Percentage		
	Preterm	Term	Adult
Total body water	85	70-75	50-60
Extracellular water compartment		40	20
Total body fat	1	15	20

2.2 Protein binding: Neonates have decreased protein binding for many drugs when compare to adults. The decrease in protein binding result in a higher free fraction for many drugs and a higher apparent volume of distribution.

3. Metabolism: Neonates have decreased activity of many enzyme pathways. Typically, if a drug's primary metabolic pathway is decreased, clearance of the drug is decreased and daily maintenance dose must be decreased or accumulation of the drug will result. This explains the decrease dosage in mg/kg/day which is required for many drugs in neonates.

4. Renal elimination: At birth glomerular filtration, tubular secretion and tubular reabsorption are all decreased in comparison to adults, thus, result in impaired drug and metaboLe elimination. Renal function matures in the following order; first glomerular filtration then tubular secretion and finally tubular reabsorption. The glomerular filtration rate (GFR) starts dramatic maturation at the gestational age of 35 weeks.[2] In premature infants GFR at birth is approximately 0.7–0.8 ml/min or about 0.5% that of an adult. A full term newborn's GFR equals approximately 2–4 ml/min.[12] Renal elimination of medicine stays prematurely during the first week of life, however, by the end of the first week, doses should be adjusted to match improving renal function. The parameters to measure renal function used in adult dosing of renally excreted drugs are not as useful in neonates and infants, since a premature infant's serum creatinine reflects more of fluid status than of renal function. For older children, the serum creatinine is useful for renal function evaluation, however, the traditional adult renal status calculation equation are not useful.[2]

Arant (1975) investigated the relationship between creatinine clearance and gestational age. This study suggests that renal functional development in the human infant is closely related to conception as illustrated in Figure 1.[13]

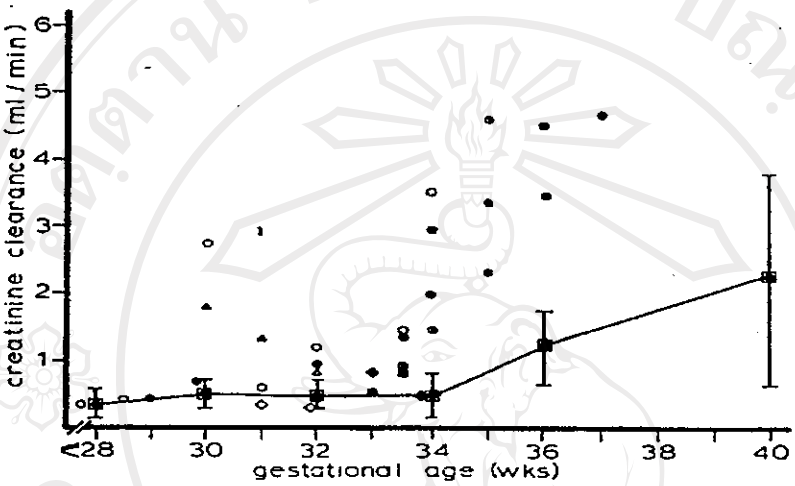

Figure 1. Relationship between gestational age (weeks) and creatinine clearance (ml/min).

Chemical structure

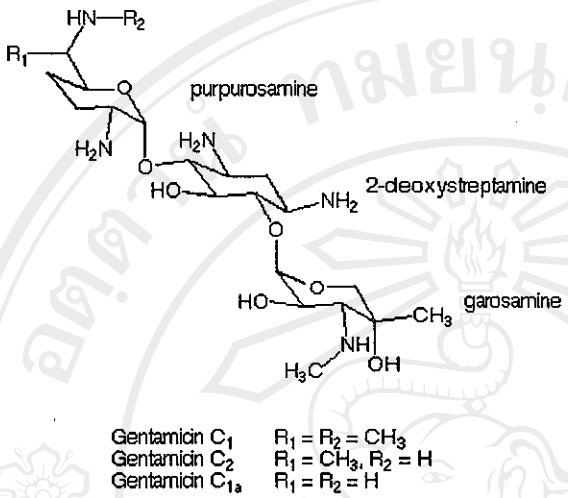

Figure 2. Chemical structure of gentamicin.

Gentamicin is an aminoglycoside antibiotic obtained from cultures of *Micromonospora purpura.* Gentamicin consist of a six-membered amino group containing ring called an aminocycLol that is linked to hexose nuclues (purpurosamine and garosamine) with glycosidic bond (Figure 2).[14] It is a complex mixture of the sulfates of gentamicin C1, C1a, C2.[15] It is most active against aerobic Gram-negative rods, but it is also used in combination with other antibiotics to treat *Staphylococcus aureus* and certain species of Streptococcus. Gentamicin was approved by US. FDA in 1966.[16]

Indication [17]

1. Pneumonia in adults and children > 5 years, together with benzylpenicillin
2. Atypical pneumonia in adults and children > 5 years, together with benzylpenicillin and erythromycin
3. Nosocromial pneumonia, together with cloxacillin or ceftazidime
4. Pneumonia due to *Staphylococcus aureus* in children aged from 2 months to 5 years, together with cloxacillin
5. Neonatal pneumonia, together with amoxicillin

6. Acute cholecystitis and acute pyelonephritis, together with ampicillin
7. Acute peritonitis, together with ampicillin and metronidazole
8. Gangrene, together with metronidazole and either benzylpenicillin or clindamycin
9. Contaminated soft tissue injuries, together with metronidazole and cloxacillin
10. Very severe pelvic inflammatory disease in adults (hospitalized patients), together with clindamycin and doxycycline
11. Infective endocarditis (initial empirical therapy), together with benzylpenicillin and cloxacillin
12. Infective endocarditis (initial empirical therapy) in patients allergic to penicillins or with nosocomial infections, and prosthetic valve endocarditis, together with vancomycin
13. Endocarditis due to ∝-haemolytic streptococci, together with benzylpenicillin or ampicillin
14. Endocarditis due to enterococci, together with benzylpenicillin or ampicillin
15. Endocarditis due to meticillin susceptible *Staphylococcus aureus*, together with cloxacillin
16. Culture negative endocarditis, together with benzylpenicillin
17. Neonatal meningitis due to unknown pathogen and neonatal meningitis due to *Listeria monocytogenes*, together with ampicillin
18. Neonatal meningitis due to group B streptococci, together with benzylpenicillin
19. Brucellosis, together with doxycycline or sulfamethoxazole+trimethoprim
20. Tularaemia and plague
21. Septicaemia (initial empirical therapy) in adults and children >5 years, together with cloxacillin or cefazolin or clindamycin or chloramphenicol
22. Neonatal septicaemia (initial empirical therapy), together with ampicillin
23. Prophylaxis in contaminated surgery, together with clindamycin

Mechanism of action

The mechanism of action of gentamicin has been generally believed to result from inhibition of protein biosynthesis by irreversible binding of the aminoglycoside to the bacterial ribosome. The intact bacterial ribosome is a 70s particle consisting of 2 subunits (50s and 30s). The smaller 30s ribosomal subunit has been identified as a primary target for gentamicin. The drug induces misreading of mRNA codons during translation as well as inhibits translocation of mRNA. However inhibition of bacterial protein synthesis does not adequately explain gentamicin's bactericidal effects, since other non-aminoglycoside antibiotics that also inhibit protein synthesis are only bacteriostatic. One aspect essential to gentamicin lethaLy is the need to achieve intracellular concentrations in excess of extracellular. Anaerobe bacteria are not susceptible to gentamicin due at least in part to a lack of an active transport mechanism for aminoglycoside uptake.[14,16]

Activity against gram-negative aerobic rods, gentamicin exhibits

1. Post-antibiotic effect (PAE) both in vitro and in vivo. The PAE refers to the continued suppression of bacterial growth despite the decline of the antimicrobial concentration to below MIC. The duration of this effect (2-8 hr) depends on several factors, chief among them is the height of the preceding gentamicin peak. The PAE phenomenon suggests that the aminoglycoside serum level may be allowed to fall below the minimum inhibitory concentration (MIC) against the pathogen without comprising antimicrobial efficacy. The PAE lasts longer in vivo than in vitro, and its duration in vivo may be dependent on host factors. Animal studies suggest that the PAE duration may be shorten by neutropenia. In addition, in vitro studies suggest that gentamicin PAE is extended by the addition of beta-lactam antibiotic.

2. The bactericidal action of gentamicin is concentration dependent, i.e, the higher peak/MIC ratio represents the higher kill rate. The multiple daily dosing regimen usually results in relatively low peak-MIC ratios (<5), but when the same total daily dose is given as a single bolus (infused over 30-60 minutes), much higher ratios are obtained (>10).

Both of these phenomena are being exploited in designing dosage regimens that employ higher doses administered at longer interval.[5]

Clinical Pharmacokinetics [3]

Gentamicin is highly polar basic compounds. It is relatively insoluble in lipids and an alkaline pH environment enhances its antimicrobial property. Binding to serum protein under normal conditions has been estimated to be between 0 and 30%.

Absorption

Gentamicin is poorly absorbed after oral administration. It is well absorbed (virtually completely) after intramuscular administration, producing peak serum levels in from 30 to 90 minutes. But the intravenous route is preferred because of the rapid attainment and predictability of the concentration versus-time profile.

Distribution

Gentamicin distribution is best described by a modified two compartment or three compartment open model, although a one compartment system is most often used. Two compartment model it is assumed that the drug distributes into two compartments, a central and a peripheral compartment (Figure 3).

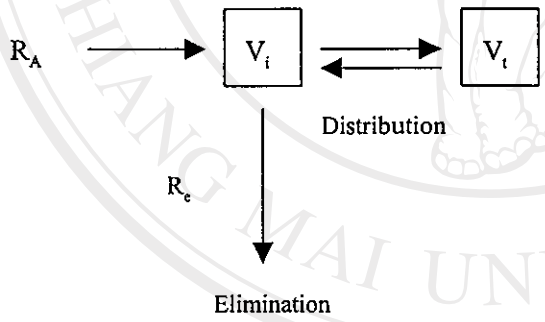

Figure 3. Two compartment model.

The central compartment represents the blood, extracellular water and highly perfused tissues (such as heart, lung, liver and kidney) and the drug is rapidly diffused in this compartment. This first compartment has a volume refer to V_i or initial volume. The peripheral compartment represents less well perfuse tissues such as muscle, skin and fat which equilibrate more slowly with the drug. This second compartment has volume refer to V_t or tissue volume. The half-life for the distribution phase is refer to the alpha (α) $t_{1/2}$, and the half-life for drug elimination from the body is refer to the beta (β) $t_{1/2}$ (Figure 4). The sum of V_i and V_t is the apparent volume of distribution (V_d). Drugs are assumed to enter into and be eliminated from V_i. That is any drug

that distributes into the peripheral compartment must re-equilibrate into central compartment before it can be eliminated.[18]

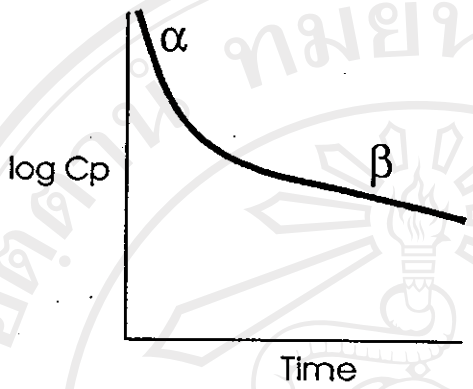

Figure 4. A drug administered into v_i follows a biphasic decay pattern. The initial decay half-life ($\propto t_{1/2}$) is usually due to drug distribution into v_t. The second decay half-life ($\beta t_{1/2}$) is usually due to drug elimination from the body.

The apparent volume of the central compartment of the two compartment model approximates the extracellular fluid volume. Following intravenous administration, distribution of gentamicin to highly perfuse organs and extracellular fluid is rapid, with the distribution phase ($\propto$) half-life range from 5 to 15 minutes and completed within 25 to 75 minutes. After the rapid phase, a second slower period (β) of decline in serum concentration begins. During the second phase the drug is being eliminated from the body and taken up by tissue. The volume of distribution (V_d) is larger in the neonates than adults and may average nearly 50% of total body weight. Adults have V_d 0.25-0.3 L/kg while neonates have V_d 0.4-0.5 L/kg. There is no correlation between V_d and PCA.[3]

Gentamicin distributes well in synovial fluid, peritoneal ascitis and pleural fluid. High concentration is obtained in renal tissue especially in renal cortex. Penetration is poor in eye and central nervous system.[19] Izquierdo et al. measured multiple linear regression, concludes that body weight has a good predictive value in estimation of the V_d in normal term neonates though the predictive value diminished in premature babies.[2]

Elimination

Gentamicin is primarily excreted unchanged through the kidney by glomerular filtration. Eighty to ninety percents of the administered dose are excreted in the urine resulting in high urinary concentration. A small amount of gentamicin is excreted by bile. At birth, the neonate renal function significantly decreases as compared with adult. Glomerular and tubular function may require several months to reach adult values. The rate of renal development is slower for the preterm neonates especially if gestational age is less than 34 weeks (Table 2).[3] Following the administration of gentamicin, its serum concentration decline in two phases. The rapid phase (α) represents distribution. The second phase half-life is 2 to 3 hr in adults and infants age > 6 months with normal renal function, and is 8 to 12 hr in preterm neonates or term with 7 days of postnatal age and reduces to 5 hr in neonates whose body weight is > 2 kg. The second phase half-life increase in proportion to a decrease in creatinine clearance.

In 1958, Kasik et al. found the correlation between PCA and half-life. The PCA was a major determinant of and infant's ability to excrete gentamicin. The relationship between half-life and decreasing PCA was exponential.[20]

In 1988, Pons et al. studied the factors influenced gentamicin plasma clearance and elimination half-life and found that gentamicin plasma clearance increases with gestational age and postnatal age but decreases as 10-minutes Apgar score decreases and as BUN increases. Both studies could predict the elimination of gentamicin in neonate and adjusted to the proper dosage regimen.[21]

Table 2. Pharmacokinetic parameters of gentamicin in preterm infants, children and adults.[3]

Age	Weight (kg)	V_d (L/kg)	$t_{1/2}$ (hr)
Preterm infants			
PCA <28 weeks	0.883	0.52	10.71
	0.937	0.65	8.80
PCA 28-34 weeks	1.435	0.51	8.25
	1.336	0.60	7.80
PCA > 34 weeks	3.01	0.50	6.04
	2.661	0.58	6.20
Terms		0.42± 0.09	4.93± 1.60
2.5 months[A]		Not report	2.90
8.7 months[A]		Not report	2.70
11.1 months[A]		Not report	2.30
29.4 ± 13.6		0.18 ± 0.08	1.6 ± 1.20
39.0 ± 10.0		0.35 ± 0.17	2.48± 0.72
76.5 ± 7.9		0.23 ± 0.12	4.43 ± 3.78
80.0 ± 6.0		0.37 ± 0.11	4.11 ± 1.39
> 80		0.22 ± 0.09	4.00 ± 2.70

[A] Mean age values

Therapeutic Range and Efficacy

The therapeutic ranges of gentamicin are correlated with achievable serum concentration and the average MIC of a sensitive organism versus level that may be associated with toxicity. Generally accepted desirable peak of gentamicin is 4-12 ug/ml and trough concentration should be less than 2 ug/ml. Higher levels are used in more seriously ill patients or when infection is present in a poorly accessible area, such as the lung (Table 3).

Table 3. Relationship between peak and trough concentration of gentamicin and treatment.

Severity	Concentration (ug/ml)	
	Peak	Trough
Moderate to severe UTI, sepsis, soft tissue infection	4-8	0.5-1.5
Severity Pneumonia, burn, live infection	8-10	1.0-1.5

The need for therapeutic drug monitoring of gentamicin is due to a correlation between measured drug concentration and therapeutic or toxic outcome.

Deziel-Evans et al. investigated the correlation of five pharmacokinetic factors with therapeutic outcome in adult patients with bacterial infections receiving aminoglycosides. Significant correlation has been found between five factors and the patient's clinical response. However, the steady state peak serum concentration ($C_{max,ss}$)/MIC ratio appeared to be the most clinically useful. A $C_{max,ss}$/MIC ratio greater than 4 results in a cure rate of 83% and a ratio greater than 8 yields a cure rate of 91%. In a retrospective studied, Moore et al. reviewed the correlation of plasma aminoglycoside concentration with MIC, indicates that the maximal peak/MIC ratio and the mean peak/MIC ratio are significantly associated with clinical outcome.[3]

Table 4. In vitro activity of gentamicin against common gram negative organism.[22]

Organism	MIC_{90} (ug/ml) of gentamicin
Escherichia coli	3.5
Enterobacter aerogenes	3.0
Enterobacter cloacae	2.5
Klebsella pneumonia	3.0
Proteus mirabilis	3.0
Pseudomonas aeruginosa	>8.0
Serratia marcescens	4.0
Acinetobacter calcoaceticus	6.0
Citrobacter freundii	3.0

Adverse Reactions

The major limiting factors in the use of gentamicin are potential nephrotoxicity and ototoxicity

1. Nephrotoxicity: Kahlmeter and Dahlager reported average frequency of nephrotoxicity resulting from gentamicin is 14%. Nephrotoxicity defined as a change in serum creatinine is a relatively late marker of aminoglycoside induced nephrotoxicity and therefore probably underestimates the true incidence of nephrotoxicity. The primary route for elimination of gentamicin is by glomerular filtration. However, a small fraction is transported and accumulated at high concentration in the proximal tubule with consequent biochemical, structural and functional alterations leading to the expression of gentamicin nephrotoxicity. The onset of acute renal failure following gentamicin treatment is usually delayed, (beginning between 7 and 10 days after therapy is started). However, early changes produced by gentamicin nephrotoxicity such as increased urinary excretion of low molecular weight proteins, and of lysosomal enzyme and brush border membrane enzymes may be detected within 24 hr. The severity and frequency of these changes depend on the dose and duration of gentamicin therapy. In addition, a rise in serum creatinine or changes in creatinine clearance are often used to determine toxicity. This is particularly important when toxicity is defined by alterations in serum creatinine that occur within 3 days of initiation of therapy.

Although gentamicin induced nephrotoxicity has been generally considered a severe adverse event, it is usually mild and reversible and rarely progresses to renal dysfunction requiring dialysis. The relationship between serum aminoglycoside concentration and nephrotoxicity has been reviewed. In one study, the initial 1-hr peak serum concentration is significantly correlated with the risk of toxicity. Dahlgren et al. noted that 36% of patients with trough concentration greater than 2 ug/ml has an increase in serum creatinine. In contrast 64% of patients with trough concentration below 2 ug/ml shows no deterioration of kidney function. Risk factors for nephrotoxicity induced by gentamicin are shown in Table 5.

Table 5. Risk factors for nephrotoxicity in patients receiving gentamicin.[3]

1. Age especially for neonate and elderly
2. Prolonged therapy risk of accumulation in kidney tissue
3. Preexisting kidney disease
4. Presence of liver disease
5. Concomitant use of other nephrotoxic drugs, cephalosporin, amphotericin B, vancomycin, cyclosporin
6. Shock
7. Prolonged high trough level

2. Ototoxicity from gentamicin is primarily a vestibulotoxic, results from an antibiotic-induced loss of sensory hair cells in the vestibular labyrinth. Vertigo, ataxia, nystagmus, nausea and vomiting may be noted in vestibulotoxic patients. Vestibular dysfunction may be reversible in up to 50% of patients and visual and propioceptive mechanism can help compensate for the deficit. Symptoms of toxicity may appear between the first and second weeks of therapy or as early as the third day of treatment. Delayed toxicity occured 10 to 14 days after stopping gentamicin therapy in patients with renal impairment has been reported. Similarly delayed vestibular toxicity presenting 3 to 6 weeks after completion of a course of gentamicin therapy has been reported. Early damage may be reversible, but if the antibiotic is continued it may be permanently damaged.[3,14,15,23] Table 6 illustrates risk factors of ototoxicity induced by gentamicin.

Table 6. Risk factor for gentamicin-induced ototoxicity.

1. Age, especially in neonate and elderly
2. Duration of treatment greater than 10 days
3. Prior exposure to gentamicin
4. Renal impairment
5. Concurrent use of diuretic
6. Total dose of drug
7. High serum peak level

3. Neuromuscular blocking action: Gentamicin can also induce muscular paralysis and respiratory depression. Basically it interferes with presynaptic release of acethylcholine or postsynaptically decrease the response to acethylcholine. Patients with myasthenia gravis, Parkinson's disease or severe hypocalcemia, infants with botulism and those receiving neuromuscular blocking agents are at risk.[3,15]

4. Hypersensitivity occurs very rarely. Some hypersensitivity reactions have been attributed to the presence of sulfite in parenteral formulation.

5. Others: Blood dyscrasias, purpura, nausea and vomiting, stomatitis and sign of liver dysfunction sush as increased serum aminotransferase values and serum bilirubin concentration.[15]

Precaution and Contraindication

Gentamicin is contraindicated for patients with known history of allergy to it. Great care is required for patients with myasthenia gravis, Parkinson's disease and other conditions characterized by muscular weakness.

Because the risk of ototoxicity and nephrotoxicity are increased at high plasma concentration, it is generally desirable to determine dosage requirement of gentamicin by individual monitoring. For patients receiving standard multiple dose regimens of gentamicin, dosage should be adjusted to avoid peak concentration above 10 to 12 ug/ml, or trough concentration exceeding 2 ug/ml. Monitoring is particularly important for patients receiving high doses or prolonged courses, infant, elderly, obese, cystic fibrosis and patients with impaired renal

function who generally require dosage reduction. Regular assessment of auditory and renal function are particularly necessary in patients with additional risk factor.[15]

Drug Administration

Dosage of drug administrations in neonates is base on gestational age, postnatal age, PCA and weight. Duration of therapy is 7 to 14 days. Doses for neonates and children are usually somewhat higher than those for adult but exact dosage recommendations vary such as

Martindale[15]

Premature neonates and those up to 2 weeks of age	3 mg/kg every 12 hr
Term neonate and children	2 mg/kg every 8 hr
Alternatively, first week of life	2.5 mg/kg every 12 hr
Neonates and infant	2.5 mg/kg every 8 hr

Keyes et al.[4]

Neonates postnatal age less than 4 days

Weight at birth 500 to 1,500 gm	2.5 mg/kg every 24 hr
Weight at birth 1,500 to 2,500 gm	2.5 mg/kg every 18 hr
Weight at birth 2,500 to 3,250 gm	2.5 mg/kg every 12 hr

Bohrman , Kliegman et al.[6]

Preterm neonates postnatal age less than 7 days

Gestational age < 34 weeks, weight at birth < 1,500 gm	2 mg/kg every 24 hr
Gestational age < 34 weeks, weight at birth > 1,500 gm	2.5 mg/kg every 18 hr
Gestational age > 34 weeks, weight at birth >1,500 gm	2.5 mg/kg every 12 hr
Term neonate postnatal age more than 7 days	5 mg/kg every 12 hr

Neonatologists' reluctance to adopt new gentamicin dosing regimens is primarily due to fears of adverse effect.[24] There are many studied suggest the larger doses per body weight and longer dosing intervals are effective and less toxic than low doses and short intervals. In 1989, Waterberg et al. studied loading dose gentamicin in 100 term and preterm neonates compared between 4 mg/kg and 2.5 mg/kg. They found that a loading dose of 4 mg/kg results in a peak

level of greater than or equal to 5 ug/ml in 92% of the patients. Forty-five patients who received 2.5 mg/kg do not achieve peak serum concentration of greater than or equal to 5 ug/ml. [25]

In 1995, Semchuk et al. compared a 4 mg/kg loading dose of gentamicin to the standard regimen of 2.5 mg/kg. All subjects (100%) in loading groups achieve an initial peak concentration greater than or equal to 5 ug/ml following the first gentamicin infusion, whereas 38.46% in standard group achieved initial peak concentration greater than or equal to 5 ug/ml. There are no significant differences between the control and loading dose groups in the number of potentially toxic serum concentration. [26]

In 1996, Isemann et al. compared initial peak and trough serum gentamicin concentrations in neonates after a standard dose 2.5 mg/kg or a loading dose 4 mg/kg on the first day of life. Standard treatment of 2.5 mg/kg gentamicin yielded initial peak serum concentration of < 5 ug/ml in neonates while a 4 mg/kg gentamicin loading dose combined with pharmacokinetic monitoring after the first dose, optimizes gentamicin therapy in neonates.[7]

In 1999, Lundergan et al. developed a simplified gentamicin dosing protocol for neonates using a loading dose and once daily dosing compared with no loading dose that included use of divided daily dosing. A loading dose followed by once daily dosing has been shown to result in serum drug level in the safe and therapeutic range in all term neonates. In low birth weight neonates, this regimen results in peak and trough concentrations similar to control group. Delaying the initiation of maintenance once daily dosing until 36 to 48 hr after the loading dose has been expected to result in a higher incidence of initial trough concentration in target range for very low birth weight neonates.[4]

In 1998, Young and Mangum published new neonatal dosing guidelines for gentamicin in a widely used drug manual "Neofax". These guidelines have been based on the cumulative adult literatures, the reported experience with loading dose in neonates and increasing number of studies of once-a-day dosing in term neonates, and pharmacokinetic data in preterm neonates. Since then, multiple studies in neonates have confirmed that pharmacokinetic indices are improving by using this approach. But no study has been large enough to confirm statistically improved therapeutic efficacy or decreased toxicity.[23] The 2002 guidelines for gentamicin in Neofax by Young and Mangum is show in Table 7.

Table 7. Dosage regimen of gentamicin in Neofax guideline

During the first week of life

Gestational age (weeks)	Dose (mg/kg/dose)	Interval (hr)
$\leq 29^{*}$	5	48
30-33	4.5	48
34-37	4	36
≥ 38	4	24

* or significant asphyxia, patent ductus arteriosus (PDA) or treatment with indomethacin

After first week of life, administer an initial dose of 4 mg/kg, then measure a peak serum concentration 30 minutes after end of infusion and another 12 to 24 hr later to determine dosing interval. [27]

Blood Sampling

For gentamicin, drug concentration is usually obtained as either peak or trough levels. Peak concentration should be drawn after distribution is complete (30 to 60 minutes after the completion of the intravenous infusion). Typical infusions are 30 to 60 minutes in duration. A trough concentration is defined as the level obtained prior to the next dose (typically within 30 minutes of the next dose). Blood samples should be obtained in the arm opposite the one in which the drug is being infused. This maneuver avoids the possible false elevation of a serum concentration due to backflow of antibiotic into the vein to be sampled. Although a one compartment model is most often used to characterize the pharmacokinetic, a multi compartment system best reflects the disposition of the agent. Peak and trough concentrations rise during therapy regardless of change in kidney function. The increase reflects tissue accumulation. For this reason, peak and trough concentrations are best obtained at steady state (3-5 dose).

Assay consideration

The one method that available for the assessment of gentamicin levels is fluorescence polarization immunoassay (FPIA). Principle of FPIA (the Abbott TDx System) uses a competitive binding immunoassay methodology, to allow tracer-labeled antigen and patient antigen to compete for binding sites on the antibody molecules. The components in this binding

reaction are the antibody, the patient antigen, and the antigen labeled with fluorescein (tracer-antigen complex). When competitive binding occur the more antigen-antibody complex then becomes a part of very large antibody molecule and consequently the less tracer-antigen complex that remains in solution.

While the tungsten halogen lamp in the TDx System emits light of different wavelengths or colors in a random spatial orientation, an interface filter located in front the light source, allows blue light (481-489 nm) to pass through. The light is then passed through a liquid-crystal polarizer to produce a beam of plane polarized blue light. The plane polarized blue light excites the tracer, or fluorophore, and raises it into an excited state. After excitation, the fluorophore returns to steady state and green light (525-550 nm) is emitted from the flurophore.

If the fluorophore is bound to a very large antibody molecule and does not rotate freely, the emitted green light will be in the same plane as the blue excitation light and polarization is retained. Conversely if the fluorophore is free to rotate because the small free tracer molecule is not bound, the emitted greenlight will be in a different plane than the blue excitation light and polarization is lost. Because of the rotational properties of molecules in solution, the degree of polarization is directly proportional to the size of the molecule. That is polarization increases as molecular size increase.

Therefore, if a patient sample contains a low concentration of antigen after a competitive binding reaction reaches steady state, there will be a high concentration of bound tracer in the reaction mixture and polarization will be high. Conversely, if there is a high concentration of antigen in the sample being tested, after the competitive binding reaction reaches the steady state, there will be a low concentration of bound tracer in the reaction mixture and polarization will be low.

The precise relationship between polarization and concentration of the unlabeled drug in the sample is established by measuring the polarization values of calibrators with known concentrations of the drug.[28]

OBJECTIVES

To determine the efficacy, safety and pharmacokinetic parameters of new dosage regimen of gentamicin adjusted dose base on gestational age according to Neofax guideline in Thai neonatal patients at the Department of Pediatric, Faculty of Medicine, Chiang Mai University.