CHAPTER I

INTRODUCTION

BACKGROUND AND RATIONALE

Children are the important population of the nation, so the problems of illness in children are the important problems of the nation.[1] Infection is a frequent and important cause of morbidity and mortality in the neonatal period.[2] Gram – negative sepsis contributes significantly to neonatal morbidity and mortality.[3]

Gentamicin is an aminoglycoside antimicrobial agent widely used in treatment of gram–negative bacillary infection in neonates.[3-5] In Thailand, as other countries, gentamicin is one of the primary antibiotic drug used for the treatment of gram–negative infection in neonates [6,7] because gentamicin is the broad spectrum antibiotic, inexpensive drug, and one of drugs in Thai national drug list. Gentamicin is among the most frequently selected agents which therapeutic drug monitoring is required due to its narrow therapeutic range and large intersubject variability in half – life and volume of distribution. Therapeutic drug monitoring has been recommended in an attempt to provide maximal potential benefit with minimal risk of toxicity.[8-12] Because of the high variability of the pharmacokinetic parameter of gentamicin in neonates makes it advisable to monitor gentamicin level in neonates.[9,13-14] Generally, when giving gentamicin 2 or 3 times/day, the accepted therapeutic maximum concentration (peak) is 4-8 mg/l [15] or 4-12 mg/l. [4,14,16-18] The minimum serum concentration (trough) should not be above 2 mg/l since high trough level persisting for prolong periods is associated with an increased risk of neprotoxicity and ototoxicity. Aminoglycoside nephrotoxicity is reversible. The incidence of ototoxicity is low, and the certain incidence is unknown. Ototoxicity has been associated with trough plasma concentration of gentamicin exceeding 4 mg/l for prolonged periods (more than ten days), [15] early damage may be reversible but if the antibiotic is continued the damage may be permanent. The

incidence of ototoxicity effects in neonates are lower than in adults.[19] When using once daily dosing (ODD), peak aminoglycoside concentration determination may not be necessary since peak concentration normally determines efficacy and this regimen has been confided that peak concentration will achieve therapeutic efficacy.[19] Trough gentamicin concentration has been often recommended below 1 mg/l when giving once daily dosing regimen.

Recently, once daily dosing of gentamicin has been introduced into clinical practice since this schedule has potential of providing a more convenient dosing interval, reduce nursing time, and may be less costly than traditional multiple daily dose schemes. This regimen may be more effective than traditional schemes since aminoglycoside show concentration dependent bactericidal activity, and they have a post antibiotic effect (PAE). The duration of PAE is depended on the aminoglycoside serum concentration achieved and the duration of exposure. It has therefore been suggested that the administration of large dose once daily could maximize the rate of bactericidal killing and could prolong the post antibiotic effect preventing regrowth of bacteria during the period of low antibiotic concentration in serum.[22-27] Once daily dosing therapy appear to be at least efficacious, no increased incidence of nephrotoxicity or otoxicity, and some studies showed less nephrotoxicity and ototoxicity.[22-33] On the basis of the large volumes of distribution and slow clearance of aminoglycoside in neonates, and the results of both in vitro and clinical studies indicated that used a once daily dosing regimen should be reasonable in full term neonates.[30-33] Gresores et al. 1994, Skopnik et al. 1995, and Hayani et al. 1997 reported the peak concentration and trough concentrations when using gentamicin 3.5-5 mg/kg once daily compared to 2.5 mg/kg twice daily in neonates with gestational ages $\geq$ 34 weeks for several days. Their studies found no incidence of adverse effects using once daily regimen for several days were no adverse effects, peak concentrations in ODD group were significantly higher while trough concentrations were not significantly different between groups.[31-33]

In Thailand, there have been very few studies of once daily dosing gentamicin, especially in Thai neonates there haven't been any reported about this regimen. This study was therefore designed to investigate the serum gentamicin levels, pharmacokinetic parameters, and pharmacological responses e.g. efficacy and toxicity

after 2.0-2.5 mg/kg of gentamicin was given twice daily as compared to the values observed after 4.0-5.0 mg/kg of gentamicin was given once daily in Thai neonates. The results obtain from this study should be useful for the improving of appropriate regimen for Thai neonates in the future.

Objectives

1. To compare the serum gentamicin levels obtained from the two dosage regimens, 2.0 – 2.5 mg/kg given twice daily and 4.0–5.0 mg/kg given once daily in neonates.

2. To compare pharmacological responses obtained from the two dosage regimen, 2.0 – 2.5 mg/kg given twice daily and 4.0–5.0 mg/kg given once daily in neonates.

3. To compare the pharmacokinetic parameters obtained from the two dosage regimen, 2.0 – 2.5 mg/kg given twice daily and 4.0–5.0 mg/kg given once daily in neonates.

Significant

1. Be able to justify whether the dosage regimen of gentamicin 2.0–2.5 mg/kg given twice daily or of 4.0 – 5.0 mg /kg given once daily will provide a suitable serum therapeutic level in Thai neonates.

2. To observe the pharmacological responses of gentamicin obtained from the dosage regimen of 2.0 – 2.5 mg /kg given twice daily or 4.0 – 5.0 mg /kg given once daily, then be able to recommend the appropriate dosage regimen for future used in Thai neonates.

3. Some pharmacokinetic parameters of Thai neonates will be provided which can be used as the data for calculating the appropriate dosage regimen for each individual patient either manually or when computer program is applied.