CHAPTER I

INTRODUCTION

Gentamicin is a broad spectrum antibiotic against *Enterrobacter species, Eseherichia coli, Klebsiella species, Proteus species, Citrobacter species, Salmonella species, Shigella species, Serratia species, Pseudomonas aeruginosa* especially gram negative aerobic bacilli but has less effect to gram positive cocci such as *Streptococcus pyrogenes, Streptococcus pneumoniae and Streptococcus viridans.* This effectiveness depends on peak serum concentration. Early studies have revealed that the effective peak serum concentration is in the range of 2 to 12 mcg / ml. For patients with negative bacilli infection such as Pseudomonas, peak serum concentration should be over 4 mcg / ml. Peak serum concentration of 8 to 10 and 5 to 8 mcg / ml are demonstrated for severe and moderate infection, respectively. Wenk (1984) have stated that the renal function of patients with serum concentration over 5 to 10 mcg / ml should be carefully monitored because reversible nephrotoxicity may occur.

Humes (1988) has stated that acute tubular necrosis (ATN) is a relatively common complication of therapy with the aminoglycoside antibiotics, wtih a rise in the plasma creatinine concentration of more than 0.5 to 1.0 mg/dl (44 to 88 μmol/L) occuring in 10 to 20 percent of patients. The renal injury induced by this drug is related to the preferential accumulation in the renal cortex. Gentamicin is filtered and then partially up by, stored in , and induce damaged to the proximal tubular cells. This prolonged storage accounts for the observation that renal failure may become clinically apparent as late as several days after the drug has been discontinued.

Pastel and Savage (1979) have demonstrated that the more distal segments also can be affected in aminoglycoside nephrotoxicity. Two major manifestation of distal dysfunction are poly urea due to decreased concentrating ability and hypomagnesemia due to enhanced urinary losses.

Magnesium depletion can lead to secondary hypokalemia and hypocalcemia. Treatment of aminoglycoside induced magnesium-wasting consists of the administration of oral magnesium supplements. However, the efficacy of this regimen is limited by urinary excretion of most of the extra magnesium.

Parker (1993) has reported that there was intriguing evidence to suggest that the frequency of dosing is also an important risk factor for the development of aminoglycoside nephrotoxicity. Studies in experimental animals suggest that the incidence of acute renal failure is diminished with high-dose, once-daily drug administration, when compared to the more traditional divided dose regimen. This protective effect is associated with diminished aminoglycoside accumulation in the renal cortex, suggesting that drug uptake by the proximal tubule is most efficient at low doses; at higher doses, more of the drug is excreted without undergoing tubular reabsorption and therfore without accumulating in the tubular cells.

Levison (1992) has shown that the higher peak plasma level with bolus therapy appears to be sufficient to promote bacterial killing, even though circulating aminoglycoside levels are relatively low most of the day.

Prins (1993) has demonstrated that several finding may well apply to humans. In one, 67 patients with serious infections were randomized toreceive gentamicin in two different dosing regimens: 1.33 mg/kg three time a day. The once-daily regimen waas at least as effective in controlling the infection as agood clinical response was observed in 91 percent of cases versus 78 percent with multiple dosees. Nephrotoxicity, defined as arise in the plasma creatinine concentration of at least 0.5 mg/dl, was much less common with single dosing, occurring in 5 percent versus 24 percent of patients. There was no difference in the incidence of ototoxicity.

The usual dosage regimen of gentamicin is recommended to be 3-5 mg/kg divided into 3 equal doses given at every 8-hour by intravenous or intramuscular administration. Now physicians in Thailand and oversea have just implemented the once daily dosing of gentamicin (one administration per day), such as 160 milligrames

once daily injection. Verpooten, Giuliano and Verbist (1989) have reported that once daily dosing of gentamicin decreased renal accumulation by giving one dose and then measuring renal cortex concentration of gentamicin by nephrectomy and extraction. The result of single once daily dose of gentamicin has already been published but the result of repeated doses for prolong therapy has not yet been confirmed. From these previous works, it is obvious that further investigation on the efficacy and safety of once daily dosing of gentamicin are needed. The main purpose of this present study was to monitor efficacy and nephrotoxicity of gentamicin obtained from once daily treatment compared to those obtained from every 8-hour treatment, to find one which option will give higher efficacy and more safety in order to improve patient outcome, reduce health care costs and decrease hospitalization stay.

Purposes of the study

1. To monitor the efficacy of gentamicin given once daily as a high dose.
2. To investigate the occurrence of nephrotoxicity caused by gentamicin when the drug was given once daily as a high dose compared to the previously recommended every 8-hour treatment.

Benefits from the study

1. Recognized the efficacy of gentamicin giving in high dose but as a once daily administration.
2. Possibly nephrotoxicity to increase quality of life in the patients.
3. Evaluate dose or dosing interval of appropriate regimen which improves patient recovery time without toxicity.
4. Establish relationship and coorperation among physician, nurse, technician , ward pharmacist and all related medical personels.
5. Capability to set up drug therapeutic monitoring unit including monitoring patient's sign and symptom when the investigator return to work at her existing hospital.