CHAPTER III

PATIENTS AND METHODS

Definition

Once-daily treatment : gentamicin 3-5 mg/kg given at every 24 hours by intravenous administration.

Every 8-hour treatment : gentamicin 3-5 mg/kg divided into 3 equal doses given at every 8 hours by intravenous administration.

The purpose of this study was to monitor efficacy and nephrotoxicity of gentamicin once-daily treatment comparing to every 8 hour treatment in the general wards of Medical Department, Rajavithi hospital between 1 June , 1995 to 31 January , 1996 by cohort study.

Patients

Up to 80 patients who enrolled in this study were the adult patients with febrile illnesses or bacterial infections and treated with gentamicin intravenously for at least 72 hours. All patients included in the study had normal renal function or mild impaired renal function with serum creatinine levels of less than 2.0 mg/dl.

Exclusion criteria were the patients with moderate to severe impaired renal function or serum creatinine levels over or equal to 2.0 mg/dl. The patients received other aminoglycosides such as amikacin, netilmicin, etc. less than 7 days were excluded from this study.

The patients, treated with intravenous gentamicin, were divided into two groups : once-aily treatment group and every 8-hour treatment group. They were matched by sex,age, body weight, prescribed dosage, indication for gentamicin treatment (infectious disease or febrile illness), severity of

disease and baseline renal function (serum creatinine and creatinine clearance).

Methods

1. Revised the patient medication profiles for recorded drug and laboratory informations

2. Investigated concept or guideline in selection of once-daily gentamicin treatment from patient medication records and interviewed the physicians about the severity of disease of that case in order to matching the appropriate pairs then recorded the information in gentamicin data record. Checked carefully about the drug interactions as showed in table 3.1.

Table 3.1 Summary of drug interactions which may occur in gentamicin therapy.

Drug interactions	Results
1. Diuretic : ethacrynic acid, furosemide, etc.	The potent diuretic may decrease extracellular fluid or be the cause of serum gentamicin increasing so the potent diuretic and dehydration may increase nephrotoxicity and ototoxicity
2. Antihistamine : dimenhydrinate , etc.	Antihistamine may conceal ototoxicity of gentamicin
3. Vancomycin	Increase nephrotoxicity and ototoxicity.
4. Cephalospoin : Cephalothin, Cephaloridine	Increase nephrotocixity
5. Anaethetics : methoxyflurane , etc.	Increase nephrotoxicity
6. Antifungal agents : amphotericin - B , etc.	Increase nephrotoxicity
7. Antineoplastic agents : cisplatin , etc	Increase nephrotoxicity
8. Immuno suppressants : cyclosporin	Increase nephrotoxicity
9. Injectable indomethacin	Increase nephrotosicity by reduce renal clearance resulting in gentamicin serum concentration increasing.
10. Depolarizing and non-depolarizing neuromuscular blocker	Neuromuscular blockage and respiratory paralysis may occur.
11. Injectable polymyxin	Increase nephrotoxicity , respiratory failure and fatigue may occur.
12. Morphine and derivativers	Neuromuscular blokage and respiratoy suppression due to synergistic action
13. Other aminoglycosides	Increase nephrotoxicity and ototoxicity

3. Divided the subjects into two groups,i.e., every 8-hour treatment group and once-daily treatment group. Measured serum gentamicin concentration since 72 hours, 30-90 minutes after the patients recieved gentamicin, and before the next dose (figure 3.1).

The trough serum gentamicin concentration of every 8-hour treatment group should be less than 2.0 mcg / ml and of once-daily treatment group should be less than 1.0 mcg / ml.

If the trough concentration is higher than the limited value and / or serum creatinine is increasing, the pharmacist will notify the physician to adjust the gentamicin dosage regimen using the patient's individual pharmacokinetic parameters. The elimination rate constance , Volume of distribution, creatinine clearance were calculated and then applied to the equations for calculating the appropriate dose.

Equation.

1. $Kd = \frac{\ln (Cp / Ct)}{t}$ hour $^{-1}$

2. $Vd = \frac{D e^{-KdT}}{Ct (1- e^{-KdT})}$ litre.

3. $MD = \frac{Vd\ Cpmin (1- e^{-KdT})}{e^{-KdT}}$ mg.

4. male: $Cl_{cr} = \frac{(140 - age)\ (weight)}{72\ (Cr_s)}$ litre/hour

5. female: $Cl_{cr} = 0.85 * \frac{(140 - age)\ (weight)}{72\ (Cr_s)}$ litre/hour

6. $Cl_{gentamicin} = Cl_{cr}$ litre/hour

7. $Vd = \frac{Cl_{gentamicin}}{Kd}$ litre

4. Monitored the efficacy of treatment by counted the number of the patients with improving outcome from

4.1 Body temperature : checked every 8 hours until stopped gentamicin administration (Normal value = 37.5 ^{o}c)

4.2 Total peripheral white blood cell count: checked every other day until stopped gentamicin administration (Normal value is less than or equal to 10,000 cell/dl.)

4.3 Bacteriologic culture response : checked every other day until stopped gentamicin administration (The culture should be negative.)

5. Monitored nephrotoxicity by checked the laboratory data especially renal function tests every other day. If serum creatinine increase from the base-line level equal or more than 0.5 mg/dl , the pharmacist will notify the physician and closely monitor the serum gentamicin concentration , signs and symptom.

Signs were checked from serum (Normal value = 1.2 mg/dl.)

Symptom that may occur are nausia and vomiting if the patient developed nephrotoxicity.

Data Analysis

1. Calculated the mean and percentage of the two groups of subjects who had serum gentamicin concentration with therapeutic level , lower than or higher than the therapeutic level , respectively.

Recorded the number of patients receiving adjusted dosage regimens.

2. Demonstated the mean, percentage and chi-square test of gentamicin efficacy.

3. Demonstated the mean duration of treatment of the two groups and compared the means by using unpaired t- test statistics.

4. Showed the frequency , percentage and chi-square test of nephrotoxicity and reported other adverse drug reactions.

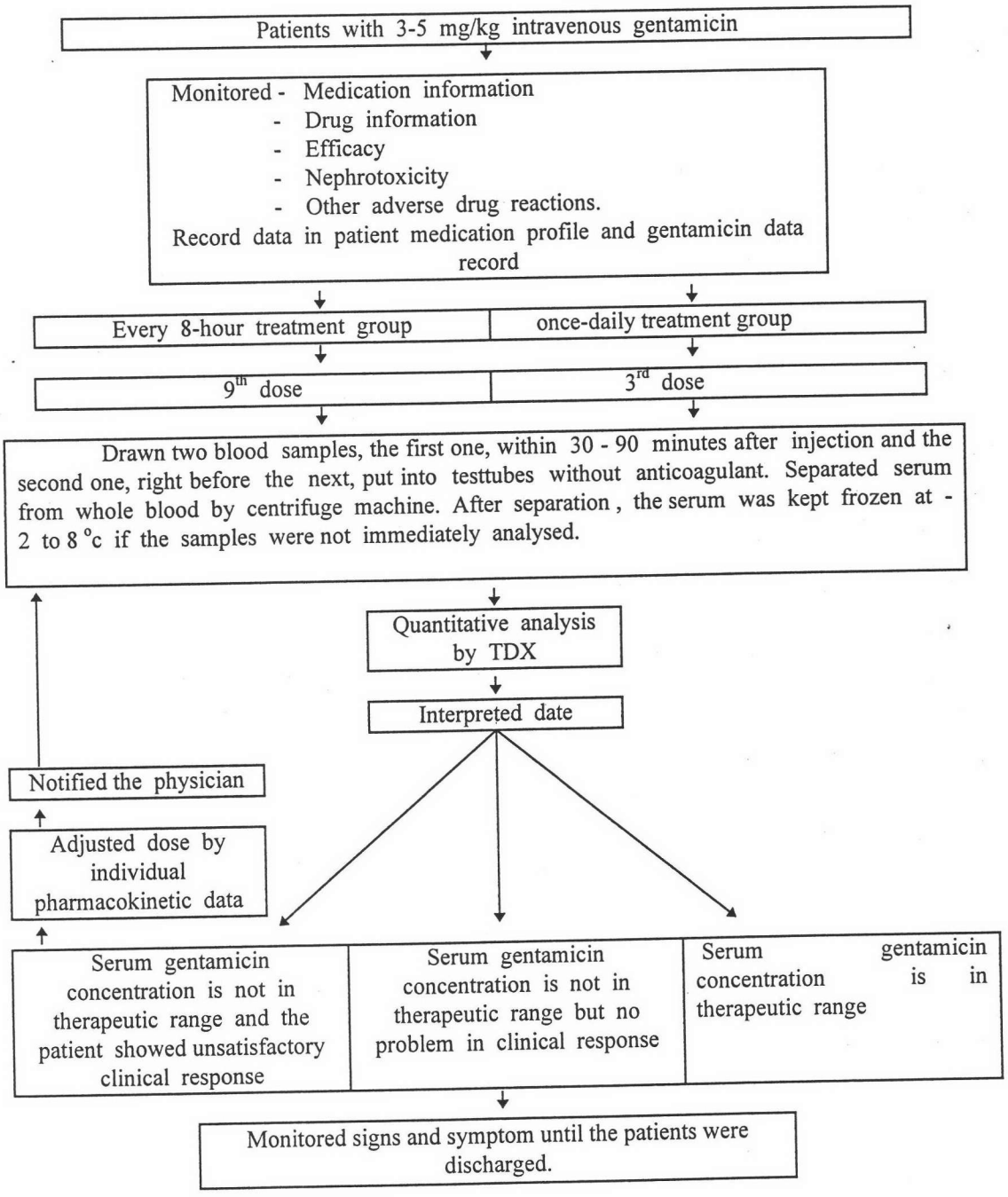

Figure 3.1 The processes of this study