Chapter I

Introduction

Gentamicin is one of aminoglycoside antibiotics which share a number of pertinent pharmacokinetic and pharmacodynamic features that have been amply discussed in several reviews and monographs (Gyselynck et al.,1971; Lietman, 1990; Simon et al.,1993; Whelton & Neu ,1992). Since their introduction into clinical use 50 years ago and despite the advent of newer agents , aminoglycoside antibiotics continue to play an important role in the treatment of severe infections (John,1988; Kovick & Yu,1991). These drugs have a wide spectrum of gram-negative activity , but possess a narrow therapeutic index.

Aminoglycoside dosage regimens are traditionally assigned according to one of the several methods. Empirical dosages based on body weight , renal function and severity of infection have been used with nomograms that provide population estimates of dosage requirements. These will be referred to as standard physician dosage adjustment methods. To optimize the use of these methods, serum concentration data points with dosage adjustments made on the basis of pharmacokinetic parameters derived by fitting these data to one compartment pharmacokinetic model (Sawchuk et al.,1977). Measuring both the peak serum aminoglycoside concentration(C_{max}) and trough serum aminoglycoside concentration (C_{min}) has been advocated by both pharmacologists and clinicians in order to ensure that therapeutic dosages are administered (Zaske et al.,1982; Wenk et al., 1984). It is essential to achieve high peak concentrations since the bactericidal activities of the aminoglycosides are concentration-dependent and the ratio of peak concentration to the MIC correlates closely with therapeutic outcome (Blaser et al., 1987; Moore,Lietman & Smith,1987). Monitoring trough concentration is also

undertaken to avoid drug accumulation which is usually the result of reduced renal elimination ; elevated trough concentrations have been associated with aminoglycoside toxicity (Wenk et al.,1984). These relationships form the basis of therapeutic drug monitoring of aminoglycosides.

Traditionally , aminoglycosides are administered in multiple daily doses (once every 8 to 12 hours). Studies of efficacy and toxicity have led to the recommendation that peak concentration should be 6 to 10 mg/L and trough concentration should be maintained below 2 mg/L for gentamicin(Burton et al., 1985; Lietman,1990).Individualized dosage regimens based on pharmacokinetic analysis have enabled these target concentrations to be achieved more efficiently than standardized or nomogram techniques (Begg et al.,1989; Erdman et al.,1991).

Recently, there has been an increased interest in simplifying therapy and in limiting toxicities of aminoglycosides by using once-daily dosing instead of conventional twice or thrice-daily dosing. Studies have indicated that once-daily dosing may be equally or less toxic than conventional regimens while maintaining equal efficacy (Fan et al.,1988; Maller et al.,1988; Hollender et al.,1989; Nordstrom et al., 1990; Ter Braak.,1990; Giamarellon et al.,1991; Prins et al.,1993; Rozdzinski et al., 1993). Once-daily dosing usually refers to a single fixed daily aminoglycoside dose which is administered intravenously every 24 hours. The promoted dose is typically equivalent to the sum of doses conventionally administered over 24-hour period, namely 3 to 7 mg/kg for gentamicin (Schumock et al.,1995).

Once-daily dosing of aminoglycosides may allow the frequency of monitoring to be reduced. Administration of the total daily dosage in one short infusion leads to peak concentrations which are at least two-fold greater than those obtained when multiple-daily doses are administered ; increasing the dosing interval to 24 hours also reduces the likelihood of drug accumulation. Nevertheless, the need for monitoring is not totally removed and remains necessary in order to detect significant

drug accumulation in patients with impaired renal function. Moreover, the peak concentrations and the area under the concentration-time curves (AUC) might be significantly different in heterogeneous groups of patients receiving standard aminoglycoside dosages because of larger inter-individual variations in the distribution and elimination of these agents (Zaske et al.,1982; Wenk et al.,1984; Rotschafer et al., 1992; Marra et al.,1996).

To date, there have been no studies which have considered the issue of monitoring serum concentrations specifically in relation to once-daily dosing regimen. Conventional target peak concentrations do not apply to once-daily dosing. Furthermore,there are various reasons indicated that monitoring trough concentration is also inappropriate for once-daily dosing. A variety of authors have recommended or implied that trough concentrations of less than 2 mg/L are acceptable when using once-daily dosing (Prins et al.,1993; Konrad et al., 1993; Ter Braak et al.,1990; Parker&Davey,1993). Others have said that 2 mg/L is too high and have suggested an upper limit of 1 mg/L for a 24-hour trough concentration (Reeves&MacGowan,1993; Bignardi&Riley, 1993). However, both of these limits are far too high based on the AUC which would accompany such trough concentrations. Patients with normal aminoglycoside pharmacokinetics would not be expected to have a trough concentration exceeding 0.05 mg/L at 24 hours (Begg et al. 1995). Predicted trough concentrations are too low to be detected by conventional aminoglycoside assay technology(Abbott Tdx, Fluorescence polarization immunoassay, limit of sensitivity 0.27 mg/L ; Syva EMIT enzyme immunoassay, limit of sensitivity 0.25 mg/L). The UK. National External Quality Assurance programme indicates that accuracy of assays for concentration below 1 mg/L is poor (Reeves&MacGowan,1993). For all of these reasons , measurement of trough concentration is not appropriate for once-daily dosing. Some authors have recognized the problems of measuring trough concentration at 24 hours and have suggested measuring concentrations at 8 - 12

hours (Reeves & MacGowan , 1993 ; Spivey & Schentag , 1990). However, pharmacokinetically- based reference concentrations to enable dose individualization were not given for these time points.

This study was designed to investigate the serum drug levels at different time points and the clinical responses of once-daily gentamicin in Thai patients , in order to determine the optimum serum sampling time for therapeutic monitoring by comparing the association between clinical efficacy and serum drug levels at different time points and comparing the association between nephrotoxicity and serum drug levels at different time points. Also , to provide pharmacokinetically - based reference concentrations to enable dose individualization for the optimum serum sampling time. In addition, this study would investigate the pharmacokinetics of once- daily gentamicin in Thai patients.

Objectives

1. To determine the optimum serum sampling time of once-daily gentamicin dosing and its relatively reference concentration for monitoring nephrotoxicity

2. To determine the optimum serum sampling time of once-dailly gentamicin dosing and its relatively reference concentration for monitoring for efficacy

Significance of the study

First , the study will provide the optimum serum sampling time for therapeutic monitoring of once-daily gentamicin dosage regimen. Second , this study will provide pharmacokinetically - based reference concentrations for the

optimum time point , including pharmacokinetics in Thai patients which might be different from those reported in foreign countries and could be used as a guide for therapeutic drug level monitoring to increase efficacy and reduce toxicity of using once-daily gentamicin dosage regimen in Thai patients.