Chapter II

Review of Literature

Review of Once-daily Gentamicin Dosage Regimen

Background

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).They have potent in vitro bactericidal activity against many aerobic Gram-negative bacilli and Gram-positive cocci. Morever, their antibacterial activity is highly concentration-dependent and does not plateau.

Since aminoglycosides are highly water-soluble , they do not cross biological membranes readily. For systemic therapy they must be given by intravenous (or intramuscular) injection. For the same reason , once in the body they are largely confined to extracellular spaces, have correspondingly small volumes of distribution (Vd) and are mainly eliminated unchanged in urine. However, penetration into cerebrospinal fluid , bronchial secretions and vitreous humour is very scanty. Thus , ordinarily , their efficacy does not extend to the latter tissues nor to intracellular pathogen.

Aminoglycosides are also endowed with a concentration-dependent liability to produce irreversible ototoxicity and reversible nephrotoxicity. Both of these toxic manifestations show a positive correlation with conventionally determined high trough concentrations (serum concentrations assessed just prior to the next dose , usually during a course of 8-hourly injection) and area under the concentration-time curves.

Collectively, their concentration-dependent efficacy and toxicity confer a narrow therapeutic index and consequently they are among the few drug classes for which therapeutic drug concentration monitoring has an established role.

Traditionally , aminoglycosides are administered in multiple daily doses(once every 8 to 12 hours).Their dosage regimens are 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).

Recently, there has been an increased interest in simplifying the therapy and in limiting toxicities of aminoglycosides by using once-daily dosing instead of conventional twice or thrice-daily dosing.

The rational for using once-daily aminoglycosides

The rational for the once-daily dosing of the aminoglycosides is based on the following observations :

1. Concentration - dependent kill rate.

Aminoglycosides appear to display concentration-dependent bacterial killing in vitro (Dudley & Zinner,1991) and in vivo (Kapusaik et al., 1988). This implies that the higher the serum concentration of the aminoglycosides , the greater bactericidal

activity against susceptible organisms. Retrospective analysis of clinical trials also supports the need for high peak concentration values to maximize clinical cure(Moore et al.,1984).

2. Post-antibiotic effect.

Aminoglycosides also possess a postantibiotic effect (PAE) , which defined as the period of suppression of bacterial growth after cessation of exposure of the bacteria to an antibiotic.The PAE theoretically protects against bacterial regrowth when serum and tissue concentrations of aminoglycosides fall below inhibitory concentration (Vogelman & Craig, 1985). The PAE of aminoglycosides has been connected to four primary factors : (a) the bacterial strains and its MIC, (b) the duration of exposure , (c) the inherent antibacterial potency and (d) the relative concentration of aminoglycoside(The higher the concentration , the longer the duration of PAE). The PAE duration for aminoglycosides ranges from 0.5 to 8 hours depending on these factors (Zhanel & Craig ,1994). Therefore , in addition to optimizing the bactericidal activity with a higher aminoglycoside concentration such as that achieves from a once-daily aminoglycoside regimen , the PAE should also be longer than with conventional regimen.

3. Adaptive post-exposure resistance.

Several in vitro studies (Blaser,1991; Begg et al.,1992) have shown that after initial administration of an aminoglycoside the bactericidal effect of subsequent doses is greatly reduced or even absent. This is due to adaptive resistance , a recently recognized phenomenon that describes reversible refractoriness to the bactericidal acton of aminoglycoside antibiotics (Daikos et al., 1990, Daikos et al., 1991). Adaptive resistance occurs with all aminoglycosides and in all Gram-negative bacilli tested to date. Studies with radiolabelled drugs have shown that aminoglycosides appear to turn off thier own energy-dependent uptake into bacteria , and this down-regulation reverses after the bacteria are not exposed to drug for a period of time (Daikos et al.,

1990). Adaptive resistance is likely to persist for long periods in peripheral compartments as a result of the persistence of aminoglycoside at these sites. These data support the use of longer dosage intervals than the conventional regimen employed , to allow time for adaptive resistance to abate so that second and subsequent doses are more effective.

4. Saturable aminoglycoside uptake into renal tubular cells.

Aminoglycosides are taken up into the kidney in the proximal tubule and accumulate in the lysosome of the cells. While in the cell , aminoglycosides inhibit lysosomal phospholipase and sphingomyelinase , which results in lysosomal phospholipidosis and accumulation of myeloid bodies and cellular necrosis. Studies in animal models have shown that renal cortical uptake of gentamicin and netilmicin is a saturable phenomenon (Giuliano et al.,1986). Study in human renal cortical cells confirmed the saturable uptake of gentamicin , netilmicin and tobramycin and suggested that the frequency of aminoglycoside administration is more important than the peak concentration in the development of nephrotoxicity (De Broe et al., 1986). These data suggest that the higher peaks do not necessarily result in a greater risk of toxicity. Although definitive evidence is still lacking , animal and human studies strongly suggest that once-daily dosage regimen is less nephrotoxic.

Clinical Studies

Efficacy

As a result of the in-vitro data and experience in animal models of infection and toxicity , once-daily aminoglycosides have been evaluated in a number of patient populations, including those with urinary tract infection , pelvic inflammatory disease , cystic fibrosis , appendicitis , and other intra - abdominal infections, Gram - negative bacteremia , bone and soft tissue infections , pneumonia , endocarditis and febrile neutropenia (Fan et al.,1988; Sturn ,1989; Nordstrom et al.,1990; Gilbert ,1991; Valcke

et al.,1992; Prins et al.,1993 ; Rozdzinski et al., 1993; Nicolua et al.,1995; Francoli et al.,1995).There are still disease states and patient populations in which once-daily aminoglycoside therapy has not been investigated or reported to an appreciable extent. These include certain Gram - positive infections , meningitis , osteomyelitis , dialysis patients , and burn patients. Most once-daily aminoglycoside studies have been conducted in Europe and have used netilmicin, alone or in combination , in doses ranging from 4.5 mg/kg to 6.6 mg/kg or amikacin , alone or combination with other antibiotics , in doses ranging from 11 mg/kg to 30 mg/kg. To date there have been many studies or reports published that have evaluated antibacterial efficacy and have used gentamicin or tobramycin , alone or in combination therapy , in doses ranging from 3 mg/kg to 7 mg/kg. These studies have demonstrated that the efficacy of once-daily dosing with aminoglycosides was at least equal to that of multiple daily dosing.

Toxicity

Clinical studies of aminoglycosides , alone and in combination with β - lactam antibiotics , have examined the potential for nephrotoxicity and ototoxicity when administered once daily. Different criteria have been used for assessing these toxicities. Nephrotoxicity has generally been defined as either an increase of 0.5 mg/dl or doubling of serum creatinine from baseline . Otovestibular toxicity has been defined in various ways. The available studies have found either no significant difference in the incidence of nephrotoxicity when comparing once-daily aminoglycosides with conventional dosage regimens (Sturn ,1989; Nordstrom et al.,1990; Rozdzinski et al., 1993; Blaser et al.,1995) or a significant difference in favour of once-daily dosage regimens (Prins et al.,1993). However , most of these clinical studies have had small sample sizes , making it difficult to assess adequately a comparatively uncommon outcome , such as aminoglycoside toxicity.

Saturation of cochlear cells might occur after the use of high dose , once-daily administration of aminoglycosides, although no studies to date have validated this theory. Other comparative studies of once-daily aminoglycosides have not all addressed the issue of ototoxicity, owing amply to the difficulty of this assessment. Furthermore , as with most studies that evaluate hearing loss, audiometric criteria have been conflicting (Sturm,1989; Viscoli et al.,1991; Vigano et al,1992.). Some investigators have merely used subjective criteria for the evaluation of hearing loss rather than audiometric testing. The issue of acceptable criteria for assessing hearing loss remains open for debate.

Very few studies have measured any neuromuscular toxicity associated with once-daily aminoglycoside administration .

It would seem to be acceptable to say that based on the available data, once-daily aminoglycoside administration is associated with a no greater incidence of the usual aminoglycoside toxicities than administration of multiple daily dosage regimen.

Selection of dosing regimen

At present , the dosage of aminoglycosides to use in a once-daily aminoglycoside strategy has not been clearly determined. In addition to deviations in the selected dose , there also have been disputed as how to alter the dosing regimen in patients with decreased drug clearances. From current data, the guideline for once-daily aminoglycoside dosage regimen can be classified in two groups.

1. Method one

The dosage regimen based on the total daily dose given in the conventional regimen and altered the dosage by using dosage de-escalation methodologies which corresponded to reduction in renal function , thereby allowing the patient to be maintained on a 24-hour dosing regimen (Gilbert, 1995; Prins et al., 1996) , as shown in table 2.1 and 2.2.

Table 2.1 Nomogram I (Gilbert,1995)

Estimated Creatinine Clearance (ml/min)	Dose (mg/kg/day)
100	5
90	5
80	5
70	4
60	4
50	3.5
40	2.5
30	2.5

Table 2.2 Nomogram II (Prins et al.,1996)

Estimated Creatinine Clearance (ml/min)	Dose (mg/kg/day)	Percentage of standard dose
$\geq$ 80	4.0	100 %
50 - 80	3.25	81 %
30 - 50	2.5	63 %
< 30	2.0	50 %

2. Method two

The dosage regimen based on achieving a target peak concentration of ten times the usual MIC of gentamicin for susceptible *P. aeruginosa* that suggested a fixed dose (7 mg/kg) and altered the dosing interval in response to variations in renal function (Nicolau et al., 1995), as shown in table 2.3 .

Table 2.3 Nomogram III (Nicolau et al.,1995)

Creatinine Clearance (ml/min)	Dose and Interval
≥ 60	7 mg/kg every 24 hr.
40 - 60	7 mg/kg every 36 hr.
20 - 40	7 mg/kg every 48 hr.
< 20	7 mg/kg , then follow serial levels to determine
	time of the next dose (level < 1)

Monitoring

The issue of optimum serum aminoglycoside concentrations after once-daily administration for the purpose of therapeutic drug monitoring has not been addressed to a great extent. Most studies have continued to monitor a peak concentration and at least one other sample concentration , either a midpoint or trough concentration (Prins et al.,1995). Others have chosen multiple samples to describe the elimination rate more accurately (MacGowan et al.,1994) or a midpoint concentration based upon population pharmacokinetics and extrapolation (Blaser et al.,1994 ; Nicolua et al.,1995). Finally , some investigators have chosen to target a particular AUC and subsequently extrapolate data from two or more serum concentrations with the assistance of computer pharmacokinetic modelling (Beg et al.,1995 ; Barclay et al.,1995).