CHAPTER III

DOSAGE AND ADMINISTRATION

Many methods have been developed to optimize aminoglycosides dosing, including use of standard doses, population-based predictive algorithms and nomograms which utilize either the serum creatinine concentration or the creatinine clearance as the index of renal function, pharmacokinetic equations, and Bayesian feedback, which utilize measured serum drug concentrations. Since these drugs have narrow therapeutic ranges and the great variability in pharmacokinetics, considerable effort has been made to develop accurate dosing methods for them. Regular monitoring of serum aminoglycoside concentrations with appropriate adjustment of dose, dosage interval, or both is often recommended. The first part of this chapter is reviewed data supporting the assumption that serum gentamicin concentration rather than dosage correlate well with clinical response. The variability of population pharmacokinetics and its effect on the relationship between dosage and serum drug concentration is also examined. In the latter part, the emphasis is on the accuracy of different dosing methods, and also on the optimum method of administration.

Predictability of Serum Concentrations of Gentamicin

If clinicians could reliably predict the serum levels of aminoglycosides on the basis of simple indices such as dose, body

weight and state of renal function, there would be little need to perform assays. The pharmacokinetic characteristics of this group of agents are relatively uncomplicated: the drugs are distributed into most of the extracellar fluid space, are minimally protein bound, and are eliminated almost solely by glomerular filtration. As a result, their serum concentrations should be fairly easy to anticipate. In fact, however, the dose-serum level profile curve of gentamicin has been found to be surprisingly unpredictable, both in terms of peak serum levels (McHenry et al., 1971; Riff and Jackson, 1971; Winters et al., 1971; Kaye et al., 1974; Barza et al., 1975; Dahlgren et al., 1975; Goodman et al., 1975; Schentag, Jusko, Vance et al., 1977b; Reymann et al., 1979) and elimination half-life from plasma (McHenry et al., 1971; Cutler et al., 1972; Kaye et al., 1974; Barza et al., 1975; Sawchuk and Zaske, 1976).

Relationships Between Dose, Serum Drug Concentration, and Response

1. Correlation of Serum Concentrations with Clinical Response

In general, serum concentrations of gentamicin correlate well with clinical response. Several investigators have attempted to discern the minimum level of antibiotic needed in the serum in order to ensure maximum efficacy. Jackson and Riff (1971), studying patients with *Pseudomonas* bacteremia, found that peak serum levels of gentamicin below 2 mcg/ml were ineffective in controlling the infection, while concentrations of 4 mcg/ml or higher were successful in all patients except those who had poor host defense

mechanisms (leukemic persons). Hewitt (1973) concurred that peak serum levels of 4 mcg/ml or greater are probably necessary for effective treatment although he cautioned that this would be difficult to verify.

Improved treatment response has been associated with obtaining therapeutic serum concentrations early in a treatment course. Noone et al. (1974) reported their experience in monitoring gentamicin therapy during the treatment of 68 episodes of serious Gram-negative sepsis in 65 hospital patients. Of those patients who were adequately treated (had peak serum concentrations of 5 mcg/ml or more in 72 hours for septicemia, urinary tract infection, and wound infection; and 8 mcg/ml or more at some time during the course of treatment for pneumonia) 84% were cured, while only 23% of the patients who had inadequate peak drug concentrations (< 5 mcg/ml) were cured. Moore, Smith, and Lietman (1984a) associated the relationship between serum aminoglycoside concentrations and efficacy in patients with Gram-negative bacteremia. Patients who initially achieved therapeutic concentrations of gentamicin (> 5.0 mcg/ml) had mortality rates strikingly less than patients with subtherapeutic concentrations (2.4% vs 20.9%).

In stead of measuring aminoglycoside concentrations in serum, some investigators have correlated clinical outcome with serum bactericidal titers (Klastersky et al., 1974; Sculier and Klastersky, 1984). Klastersky et al. (1974), in a study using gentamicin and other antibiotics for septicemia and both wound and respiratory infections, noted that clinical success was 67% and > 80% among 317 patients when the peak titer of bacteriostatic activity in

the serum was equaled or exceeded 1:4 and 1:8 (i.e., the peak level exceeded the minimum inhibitory concentration by fourfold and eightfold), respectively. Moore, Lietman, and Smith (1987), in an examination of the relationships among plasma aminoglycoside concentrations, the minimal inhibitory concentrations (MIC) for the infecting organism, analyzed data from 236 patients with Gram-negative bacterial infections who were participants in four previously reported randomized, double-blind, controlled clinical trials of gentamicin, tobramycin, and amikacin (Smith et al., 1977, 1980, 1985; Wade et al., 1978). Elevated maximal and mean peak aminoglycoside concentration/MIC ratios were strongly associated with clinical response ($P < .00001$ and $P < .0001$, respectively). The trough and the geometric mean aminoglycoside concentrations were not as strongly associated with clinical response. A graded increase in the rate of clinical response for increasing maximal peak concentration/MIC ratios was found. By logistic regression the peak concentration/MIC ratios were associated significantly with clinical response after adjustment for underlying severity of illness and other factors correlated with response. These results indicated that a high peak concentration relative to the MIC for the infecting organism is a major determinant of the clinical response to aminoglycoside therapy.

2. Correlation of Serum Concentrations with Toxicity

Ototoxicity and nephrotoxicity are the major adverse effects of aminoglycosides. Most clinicians accept a relationship between serum drug concentration and toxicity and try to avoid high

peaks and sustained, elevated trough concentrations. Although these adverse effects have been suggested to be associated with peak serum concentrations of gentamicin exceeding 10 to 12 mcg/ml and trough concentrations above 2 mcg/ml (Dahlgren et al., 1975; Goodman et al., 1975), some consider that neither concentration has proved to be a reliable indicator for toxicity (Wenk, Vozeh, and Follath, 1984).

2.1 Correlation of Serum Concentrations with Nephrotoxicity

Broadly speaking, aminoglycoside nephrotoxicity is a dose-related phenomenon. However, there is considerable uncertainty concerning the relative importance of the total dose, duration of therapy, and serum levels. Some authors ascribe toxicity primarily to the presence of excessively high peak levels in the serum, and others to the absence of a sufficiently low trough. The results of some pertinent studies are summarized in table 5.

Dahlgren et al. (1975) found a correlation between increasing trough levels of gentamicin and nephrotoxicity. They reported that 8 of 21 patients (38%) with trough gentamicin levels greater than 2 mcg/ml, 2 of 6 with trough levels above 3 mcg/ml, and 5 of 5 with trough levels above 4 mcg/ml developed a rise in serum creatinine. This did not occur in 64 patients with trough gentamicin levels less than 2 mcg/ml. In contrast, only 1 of 5 patients with peak levels > 10 mcg/ml experienced nephrotoxicity.

Goodman et al. (1975) prospectively compared the rates of gentamicin nephrotoxicity in a small number of patients treated by variable dosage or by variable frequency regimens.

Table 5. Correlations Between Peak and Trough Serum Concentrations of Gentamicin and Toxicity

Reference	Nephrotoxicity		Ototoxicity		Comment
	Trough	Peak	Trough	Peak	
Dahlgren et al. (1975)	Implied correlation	No correlation	-	-	Correlation with trough levels not statistically significant, but only a small number of patients study
Goodman et al. (1975)	Significant ($p = 0.027$)	No correlation	-		High trough levels could be an early indication of renal damage rather than the cause of it
Nordstrom et al. (1973)	-	-	Significant ($p < 0.05$)	No correlation	Patients with ototoxicity had significantly higher serum creatinine concentrations and longer duration of therapy
Tjernstrom et al. (1973)	-	-	-	No correlation	86% of patients who developed vestibular damage had pre-existing ototoxicity. None had serum peak > 10 mcg/ml
Banck et al. (1973)	-	-	Implied correlation	No correlation	Studied a group of patients who had received prior ototoxic antibiotics, had renal insufficiency, were treated for a prolonged period or had received a large total dose of drug
Cox (1969)	-	-	-	Implied correlation	Of the 3% who developed ototoxicity with high serum levels of gentamicin, 67% were uremic
Jackson and Arcieri (1971)	-	-	-	Impiled correlation	Peak levels were not determined in all patients. There was a significant correlation ($p = 0.003$) between ototoxicity and renal dysfunction

from Barza and Lauermann 1978. Clin. Pharmacokin. 3: 202-215.

Deterioration of renal function occurred with similar frequency in both groups. The only significant predictor of nephrotoxicity was a trough level of gentamicin > 4 mcg/ml; this occurred in each of 7 individuals who exhibited a subsequent rise in serum creatinine concentration, but in only 3 of 9 without such a rise ($p = 0.027$). Barza and Lauermann (1978) discussed that in both this study and that of Dahlgren et al. (1975), the occurrence of high trough levels before the onset of nephrotoxicity could be interpreted as an early sign of renal damage rather than the cause of it.

Schentag et al. (1977a) reported greater increases in trough serum drug concentration in patients experiencing nephrotoxicity than in those without nephrotoxicity, though this observation could not distinguish cause from effect.

Moore and colleagues (1984c) demonstrated that aminoglycoside concentrations were one of the major determinants of nephrotoxicity along with age, sex, occurrence of shock, baseline renal function and hepatic impairment. They analyzed the course of Gram-negative infection and tratment in 214 patients who had received either gentamicin or tobramycin in randomized prospective clinical studies. In the control group without aminoglycoside therapy, a 50% reduction in creatinine clearance (the criterion of nephrotoxicity) was observed only once; however, this side effect occurred in 30 (14.1%) patients receiving gentamicin or tobramycin. After investigation and statistical evaluation of various co-factors, the following circumstances were found to be significantly

associated with nephrotoxicity. In the group that showed toxicity, the peak serum level of 7.2 ± 0.4 mcg/ml was higher than in the group without toxicity, which had a level of 5.3 ± 0.1 mcg/ml. The trough level of 3.4 ± 0.3 mcg/ml in the group with toxicity was also higher than the trough level of 2.6 ± 0.1 mcg/ml in the group without side effects. Patients who experienced toxicity had a higher creatinine clearance before therapy. It is possible that the higher initial drug "flooding" to the tubular cells contributed to the development of nephrotoxicity. Some of the affected patients also had hepatic disorders, suggesting a connection between hepatic insufficiency, reduced renal blood flow, and activation of the renin-angiotensin mechanism. Shock states occurred more commonly in the group with toxicity and led to reduced organ perfusion. Finally, women were affected more often than men.

In addition, studies of aminoglycoside nephrotoxicity in experimental animals show greater toxicity from sustained, high trough concentrations (Bennett et al., 1979; Powell et al., 1983).

2.2 Correlation of Serum Concentrations with Ototoxicity

Studies in rats, guinea pigs (Federspil Schatzle, and Tiesler, 1976), and cats (Waitz, Moss, and Weinstein, 1971), have shown that a single daily dose of aminoglycoside is more ototoxic than the same quantity given in divided doses. This is in contrast to the situation previously described with regard to

nephrotoxicity. However, it has been difficult to establish a correlation between high serum peaks and ototoxicity in man (Jackson and Arcieri, 1971; Banck et al., 1973; Nordstrom et al., 1973; Tjernstrom et al., 1973).

There has been a longstanding suggestion that high trough levels of gentamicin predispose to eighth nerve damage (table 5) (Banck et al., 1973). In a prospective study, Nordstrom et al. (1973) found a significant relationship between elevated trough levels of gentamicin and ototoxicity. However, renal impairment may have played a contributory role, and the total dosage and duration of therapy were greater in the group with auditory damage.

The data from 135 patients receiving gentamicin and tobramycin were analyzed by Moore, Smith, and Lietman (1984b) with reference to ototoxicity. The total dose of aminoglycoside received was higher in the group in which impaired hearing developed. This group had received 3.06 $\pm$ 0.37 grams of aminoglycoside, compared with 2.01 $\pm$ 0.15 grams in the group without side effects. The duration of therapy also differed. The group with side effects received aminoglycosides for 9.1 $\pm$ 0.8 days, compared with 6.6 $\pm$ 0.1 days for the group without side effects. Patients with ototoxicity also had higher fever initially. It was suspected in these cases that the cytoprotective prostaglandins of class E are produced in smaller quantities under the influence of fever and aminoglycosides. More patients with ototoxicity had an initial bacteremia that could lead to direct cochlear injury by bacterial endotoxins and/or

changes in the endolymph caused by these toxins. The peak and trough levels of aminoglycoside were, in contrast to the situation with nephrotoxicity, not signifantly associated with the development of ototoxicity. This observation is in disagreement to some extent with the studies of Wilson and Ramsden (1977), who described a reversible cochlear damage with peak tobramycin concentrations above 8 to 10 mcg/ml.

In general, to optimize response with aminoglycoside antibiotics and avoid toxicity, intermittent dosing appears best, because it provides peak serum drug concentrations which kill or inhibit bacteria, yet allows descent to trough concentrations which will presumably minimize renal accumulation of and toxicity from gentamicin. Most clinicians would agree that peak concentrations of 4 to 10 mcg/ml and troughs of < 2 mcg/ml satisfy these criteria (Burton, Vasko, and Brater, 1985b).

3. Relationship Between Dose and Serum Concentrations

Many studies have noted that doses of gentamicin correlate poorly with serum concentrations. Correlations of dose to serum drug concentration for some studies are summarized in table 6.

Winters et al. (1971) found that a standard dose of 1 mg per kg produced peak serum drug concentrations from 2.1 to 5.0 mcg/ml. Riff and Jackson (1971) reported that doses of 1.5, 3.0, and 4 to 6 mg/kg/day produced trough serum concentration ranges of 0.5 to 3.5, 0.5 to 8.0, and 0.5 to 15 mcg/ml and peak serum concentration ranges of 1 to 8, 1 to 16, and 2 to 16 mcg/ml, respectively.

Table 6. Correlations of Dose to Serum Concentration of Gentamicin

Reference	No. of patients	Correlation coefficient	p value	Concentration
Kaye et al. (1974)*	23	0.79	< 0.01	Peak
Barza et al. (1975)	19	0.762	< 0.001	Peak
Goodman et al. (1975)	20	0.60	< 0.01	Increment (peak-trough)
Schentag et al. (1977b)	47	0.25	< 0.1	Peak
Reymann et al. (1979)**	120	-0.150 to 0.318	0.172-0.811	Peak

* Patient with creatinine clearance greater than 90 ml/min had an excellent correlation.

** Correlation coefficients represent 5 patient groups which had dose and serum concentrations compared based on a method dosing which uses estimated renal function.

Kaye and co-workers (1974) studied 23 patients in whom a gentamicin serum concentration of 5 mcg/ml was attained one hour after intramuscular injection of doses ranging from 0.9 to 2.35 mg/kg body weight. A dose of 2.35 mg/kg body weight given to two different patients yielded extremely different peak concentrations of 5.2 mcg/ml and 14 mcg/ml.

Barza et al. (1975) measured peak serum concentrations in 19 patients after intravenous or intramuscular administration of gentamicin at 1.2 to 1.7 mg/kg body weight, and found that levels ranged from 1.7 to 7.4 mcg/ml. Goodman et al. (1975) measured trough and peak serum concentrations and found, in agreement with other authors, a high degree of variability among patients. Moreover, patients given identical doses showed different serum concentrations at different times.

From these data, it is clear that the relationship between doses of gentamicin and serum drug concentrations in general is poor. Interestingly, the more patients studied, the poorer the correlation. Thus, administering a "usual" dose of gentamicin cannot be expected to achieve a specific serum drug concentration in individual patients (Zaske et al., 1982b).

A number of factors influence the relationship between gentamicin dose and serum drug concentration including renal function, obesity, age, fever, degree of hydration, concurrent therapy with penicillin analogues, burns, diseases, and other unknown variables (Gyselynck et al., 1971; Barza and Lauerman 1978; Yee and Evans, 1981).

4. Summary

In summary, considerable data demonstrate the poor relationship of gentamicin to serum drug concentration and a better relationship of serum drug concentration to response assessed as either efficacy or as toxicity. It follows that dosing stratagies should attempt to achieve target serum drug concentrations rather than using a "standard" dose.

Dosing Methods

1. Standard Doses

The usual IM or IV dosage of gentamicin recommended by the manufacturers for adult patients with normal renal function is 3 mg/kg/day given in three equally divided doses every 8 hours (Zaske, 1980; Gennaro, 1985; McEvoy, 1989; Reynolds, 1989). The manufacturers state that in life-threatening infections up to 5 mg per kg may be administered daily in 3 (Zaske, 1980) or 4 equally divided doses (McEvoy, 1989; Reynolds, 1989), or 1.7 mg/kg of body weight every 8 hours (Gennaro, 1985); dosage should be reduced to 3 mg/kg daily as soon as clinically indicated (McEvoy, 1989). For urinary infections, adults whose body weight less than 60 kg may be given 3 mg/kg once a day or 1.5 mg.kg every 12 hours (Gennaro, 1985). Children may receive 5 (Reynolds, 1989) or 6 (McEvoy, 1989) to 7.5 mg/kg/day (Gennaro, 1985; McEvoy, 1989; Reynolds, 1989) given in equally divided doses at 8-hour intervals. Infants and neonates should receive 7.5 mg/kg/day given in equally divided doses at 8-hour intervals; premature or full-term neonates 1 week of age or less should be given 2.5 mg/kg every 12 hours (Gennaro, 1985; McEvoy,

1989). The course or treatment should generally be limited to 7 to 10 days (Reynolds, 1989). As gentamicin is poorly distributed into fatty tissue, some authorities suggest that the dosage calculations should be based on an estimate of lean (Reynolds, 1989) or ideal body weight (McEvoy, 1989).

Because of the constraints placed on gentamicin dosage due to the drug's narrow therapeutic index and high dependence on renal excretion, patients with renal impairment will rapidly accumulate blood levels to potentially toxic concentrations if normal dosage regimens are maintained. Thus, in patients with renal insuffiency, dosage should be reduced for various degrees of renal impairment.

From the previous section, it is obvious that the use of "standard" doses to effect desired clinical response is unreliable in many patients. This fact has led to the development of methods for individualization of drug therapy, including predictive nomograms, pharmacokinetic methods, and a Bayesian feedback method.

2. Predictive Algorithms

Most nomograms have been developed using small populations of patients to determine the relationship between drug pharmacokinetics and one or more clinical parameters such as renal function. This derived relationship is then supposed applicable to large groups of patients. Unfortunately, the groups from which the data are derived are often relatively homogenous; consequently, data from them extrapolates poorly to the population as a whole. Thus,

nomograms can continue to serve as a starting point for therapy, but their inaccuracy limits their utility. In addition, development of newer, more accurate methods using measured serum drug concentrations has relegated nomograms to a "first step" or "back up" status.

Although nomograms can be used as starting points for drug therapy, they are generally based on invalid assumptions and their error in achieving a target serum drug concentration is considerable (Lesar et al., 1982). For example, most nomograms use a statistical relationship between aminoglycoside elimination and measured creatinine clearance. The minimal information needed to use aminoglycoside dosing nomograms includes a patient's age, sex, weight, and serum creatinine concentration or creatinine clearance. Several investigators have found that aminoglycoside elimination half-life often correlates poorly with serum creatinine levels and estimates of creatinine clearance (Kaye et al., 1974; Barza et al., 1975). Although nomograms are based on measured creatinine clearance, most clinicians usually substitue a calculated creatinine clearance. Some have stated that only 38% of the variance (r^2) in elimination rate was explained by differences in creatinine clearance (Lesar et al., 1982). Thus, other factors that are related to aminoglycoside disposition are not included in nomograms. This discrepancy reduces the usefulness of the statistical relationship between aminoglycoside elimination, creatinine clearance, and dosage calculation. Other important aspect is that most nomograms assume a constant volume of distribution and thereby have limited predictive

ability when the patient's disease, drug interactions or other factors change volume of distribution.

A variety of methods have been developed to achieve desired peak and trough gentamicin serum concentrations. In earlier times, attempt has been made for modifying dosage regimens during various stages of renal impairment, then it is applied to optimize therapy in individual patients. Several methods used to modify dosage regimens for gentamicin are presented in table 7.

One of the earliest methods was that of McHenry et al. (1971), a modification of kanamycin described earlier by Cutler and Orme (1969), which is commonly referred to as the *"rule of eights"*. In 24 patients, McHenry et al. (1971) found that gentamicin half-life correlated closely with serum creatinine (r = 0.94) and that half-life was approximately equal to the serum creatinine value times 4. With data from the same 24 patients, they developed a predictive algorithm and tested the method in 5 actual and 2 hypothetical patients. It was found that 2 times the predicted gentamicin half-life produced the best gentamicin peak and trough serum concentrations. Thus, the "rule of eights" refers to the administration of a "normal dose" of aminoglycoside to patients at a dosing interval equal to the serum creatinine times 8. This method then alters the frequency of administration while maintaining a constant dose and has also been called the variable frequency method.

Chan et al. (1972) subsequently published a nomogram for gentamicin dosing. This method was based on data in 17 patients in

Table 7. Methods used for modifying gentamicin dosage regimens

Authors	Methods*
Gingell and Waterworth (1968)	Loading dose of 1.1 mg/kg; maintenance doses from a table in the published paper.
Jelliffe et al. (1970)	Loading and maintenance doses provided by computer-based input variables such as blood level desired, dosing interval desired, renal status, age, weight, and sex.
McHenry et al. (1971)	Loading dose of 1.1 mg/kg; maintenance doses of 1.1 mg/kg every 8 S_{cr}.
Chan et al. (1972)	Loading dose of 1.7 mg/kg; maintenance doses from a nomogram in the published paper.
Cutler et al.-1 (1972)	Loading dose of 2.0 mg/kg; maintenance doses of 1.0 mg/kg every 4 S_{cr}.
Cutler et al.-2 (1972)	Loading dose of 2.0 mg/kg; maintenance doses of 2.0 mg/kg every 9-12 S_{cr}.
Schumacher (1973), and Giusti and Hayton (1973)	a) Prolonged dosing interval method - normal loading dose of 1.7 mg/kg at a dosing interval prolonged over the normal in proportion to the increase in half-life value. b) Reduced dose method - normal dosing interval of eight hours with maintenance doses decreased from the normal dose of 1.7 mg/kg in proportion to the increase in half-life values; loading dose calculated from the maintenance dose using equations in the cited references.
Dettli (1974)	Loading dose of 1.7 mg/kg; maintenance doses of approximately one-half of the loading dose administered at a convenient dosing interval close to the half-life during renal impairment.

* S_{cr} = Serum creatinine concentration.

whom the dosing interval was maintained at 8 hours while altering dose based on renal function. These authors found a linear relationship between the elimination rate constant (k_{el}) and creatinine clearance (Cl_{cr}) up to values of 70 ml/min·1.73 m^2 body surface area; when the Cl_{cr} was 70 ml/min or more the k_{el} was normal (remained constant). In effect, they selected a Cl_{cr} of 70 ml/min as "normal" for gentamicin dosing. As a consequence, this method resulted in administering greater total amounts of drug than previous methods. They noted the successful use of this method in all of 17 patients with life-threatening Gram-negative bacterial infections and attributed this success to the use of the variable dose regimen as opposed to the variable frequency regimen, even though their study was not a direct comparison. In a subsequent study, Churchill et al. (1978) examined the accuracy of the Chan et al. guidelines in 22 courses of therapy given to 18 patients with creatinine clearances ranging from 6 to 65 ml/min. The Chan nomogram produced mean peak gentamicin concentrations of 6.4 mcg/ml (range 4.5 to 11.9 mcg/ml) and mean trough gentamicin concentrations of 3.6 mcg/ml (range 0.9 to 7.8 mcg/ml). Only 2 of the 18 patients had trough concentrations less than 2 mcg/ml. A fairly good correlation was found between observed and predicted peak ($r = 0.70$) and trough ($r = 0.67$) serum drug concentrations. However, the clinical relevance of these correlations is unclear, since a wide range of serum drug concentrations was attained.

Mawer et al. (1974) published a nomogram using a variable frequency regimen and programmed a small digital computer

to perform the calculations. In 36 patients compared with 29 controls dosed according to physician intuition, the nomogram successfully achieved desired peak concentrations (3 to 10 mcg/ml) in all of 36 patients compared with 20 of 29 controls. There was a good correlation ($r = 0.88$) between the observed and predicted gentamicin concentrations.

Schumacher (1975) reassessed various methods used for modifying gentamicin dosage regimens (Table 7) by applying pharmacokinetic techniques to eight prototype cases of renal impairment (serum creatinine range of 0.9-12.0 mg/dl and creatinine clearance range of 5-100 ml/min/1.73 m^2). These methods use either the serum creatinine concentration or the creatinine clearance as the index of renal function. As shown in table 7, the methods of Gingell and Waterworth (1968), McHenry et al. (1971), Chan et al. (1972), and Cutler et al. (1972) stipulate the dosage to be used; the methods of Cutler and McHenry use fixed doses with dosing intervals computed by multiplying the stable serum creatinine value by a constant. The method of Jelliffe et al. (1970) calculates the dosage on the basis of the dosing interval and the blood level desired by the clinician; concentrations of 5 mcg/ml and 8 mcg/ml were chosen as variables. The half-life method (Dettli, 1974) and the method of Schumacher (1973) and Giusti and Hayton (1973) modify dosage on the basis of the "normal" dose chosen by the clinician; a dose of 1.7 mg/kg every eight hours (5.1 mg/kg/day) was selected on the basis of the previous clinical observations (Darrell, 1972; Wise and Reeves, 1972; Hewitt, 1973; Riff, 1973; Mawer et al., 1974;

Noone et al., 1974). The author concluded that methods based on creatinine clearance as index of renal function generally achieved greater percent duration of the dosing interval above the effective response concentration of a 4 mcg/ml blood level and lesser duration of blood levels below this value than methods based on serum creatinine. The reason for this is that serum creatinine is a most indirect index of kidney function. Similar serum creatinine values in patients of different sex, weight, or age can represent markedly different levels of renal function. In addition, serum creatinine as an index of kidney function is least accurate when kidney function is most impaired. Creatinine clearance is recognized as a much more accurate index of renal function and it does account for sex, weight and age.

Hull and Sarubbi (1976), Sarubbi and Hull (1978), and Dettli (1974) formulated what many consider to be the best predictive algorithms for aminoglycoside therapy. The Hull and Sarubbi method is designed to maintain a desired maximum serum concentration of aminoglycoside, to modify both dose and dosing interval to compensate for changes in renal function, and to minimize toxicity secondary to high, sustained trough concentrations. In addition, these authors suggested dosing aminoglycosides based on lean body weight. This concept has also been supported by Reymann et al. (1979) who found a better correlation (r = 0.626) between dose and peak serum aminoglycoside concentration when dose was administered per kg of ideal body weight compared with the poor correlation (r = 0.15 to 0.32) when using actual body weight.

The first nomogram of Hull and Sarubbi (1976) established dosing guidelines for gentamicin, while their second could be used for kanamycin, amikacin, gentamicin or tobramycin (Sarubbi and Hull, 1978). The relationship they derived for individualization of gentamicin pharmacokinetics assumes a volume of distribution of 0.26 L/kg of lean body weight and an elimination rate constant of 0.0024 times the creatinine clearance plus 0.01. To evaluate the gentamicin nomogram prospectively, 32 serum samples were obtained in 16 patients with varying degrees of renal function who had been dosed using the nomogram. The mean predicted serum drug concentration ($\pm$ SD) was 6.4 $\pm$ 1.0 mcg/ml while the measured concentration was 5.8 $\pm$ 1.2 mcg/ml. No data were presented to assess the accuracy or precision of the method. To evaluate the amikacin nomogram prospectively, 25 serum samples were obtained in 10 patients. The measured peak amikacin concentration ($\pm$ SD) was 25.5 $\pm$ 6.1 mcg/ml compared with a predicted peak concentration of 23.6 $\pm$ 4.6 mcg/ml. Again, individual data were not assessed for accuracy and precision. Retrospective analysis of the second Sarubbi and Hull nomogram showed excellent correlations between predicted and actual serum concentrations for gentamicin (130 serum concentrations in 40 patients; $r = 0.90$) and amikacin (153 serum concentrations in 26 patients; $r = 0.88$). Mean gentamicin peak and trough serum concentrations ($\pm$ SD) were 6.7 $\pm$ 2.6 mcg/ml and 2.9 $\pm$ 1.8 mcg/ml, respectively.

The nomogram developed by Dettli (1974) modifies both dosage and frequency and may be used for aminoglycosides and other

drugs eliminated primarily by renal excretion. This nomogram is based on a 1-compartment pharmacokinetic model for modification of a normal dose based on population characteristics. It assumes that nonrenal clearance is not affected by renal dysfunction. Data have not been presented to authenticate performance.

When each of the predictive dosing guidelines was first published, considerable accuracy was demonstrated or implied, possibly due to the fact that validation was usually assessed in small, homogenous patient groups. Unfortunately, these data do not extrapolate to more general patient populations. It is apparent from studies in large groups of patients that there is considerable interindividual variability in the handling of aminoglycosides. Table 8 presents data in over 1700 patients with normal and abnormal renal function demonstrating the tremendous variability in dose and dosing interval required to achieve target concentrations. It is important to re-emphasise that all previously discussed algorithms assumed a constant volume of distribution for aminoglycosides, particularly gentamicin. This is obviously invalid; therefore, one might have predicted poor performance of these guidelines when applied to large patient groups.

3. Pharmacokinetic-Based Dosing Methods

Pharmacokinetic models, initially developed to describe the behavior of drugs in man, can also be used to predict the serum drug concentration that will result from a dosage regimen. To do this, however, certain pharmacokinetic parameters must be known or

Table 8. Variability in gentamicin dosing requirements in patients with normal and abnormal renal function to achieve therapeutic serum concentrations

Reference	No. of patients	Patient type	Daily dose range (mg/kg)	Dosing interval (h)
Zaske et al. (1976)	14	Burn	5.28-30.0	Not given
Zaske et al. (1980a)	242	Surgical	0.7-12.4	4-48
Zaske et al. (1980b)	67	Obstetrical	3.0-11.6	4-8
Zaske et al. (1981)	249	Gynecological	1.9-14.0	4-12
Zaske et al. (1982b)	1640	Gram-negative infection	0.4-25.8	4-48
Zaske et al. (1982c)	417	Geriatric	0.3-22.0	4-48
Bauer and Blouin (1983)	30	Obese (normal)	540*	8
	30	Normal	380*	8

from Burton, Vasko, and Brater 1985a. Clin. Pharmacokin. 10: 1-37.

* Mean value in mg; ranges not given.

at least be accurately estimated. Some pharmacokinetic methods use several serum drug concentrations following a test dose of drug to describe the pharmacokinetics of the drug in an individual patient. As one might expect, these methods are quite accurate (Lesar et al., 1982), but have several limitations. They require serum drug concentration data early in therapy and anytime thereafter if pharmacokinetic parameters change. For example, if a patient has changing renal function, a new test dose of drug followed by appropriate serum drug concentrations must be used to re-estimate pharmacokinetic parameters each time renal function changes. In addition, the methods that have been developed are labor intensive, requiring specialized personnel or consulting services for their implementation. This, including the necessity of multiple serum samples, is expensive and therefore must have considerable impact on the quality of patient care to be cost effective.

Critical assessment of the performance of dosing methods in large groups of heterogenous patient populations is important before accepting reliability. A study of 96 such patients (Lesar et al., 1982) compared the methods of Sarubbi and Hull, Dettli, McHenry, and Chan to an individualized pharmacokinetic method (Sawchuk et al., 1977). The Sawchuk and Zaske method uses 3 serum drug concentrations after infusion of a test dose, and also a predose sample from patients receiving gentamicin before the test dose, to calculate the individual's pharmacokinetic parameters and then a dosing regimen. As shown in table 9, a wide range of steady-state peak and trough concentrations were calculated for each dosing method in all

Table 9. Comparison of the ability of 5 dosing methods to achieve desired peak and trough serum concentrations.

Dosing Method	Peak concentration (mg/L)*		Trough concentration (mg/L)*		% of patients with peaks 6-10 mg/L and troughs < 2 mg/L
	mean ± SD	range	mean ± SD	range	
Sarubbi-Hull					
Every 8 hours	5.8 ± 1.9	2.3-10.5	1.25 ± 1.2	0.1-6.4	28
Every 12 hours	6.0 ± 1.8		0.8 ± 1.3		26
Every 24 hours	5.9 ± 1.6		0.5 ± 0.9		24
Dettli	5.6 ± 1.6	2.7-11.2	0.8 ± 0.5	0.2-2.6	43
Rule of eights	5.8 ± 1.7	2.8-12.2	1.0 ± 0.9	0.1-5.3	28
Chan	6.4 ± 2.1	2.4-12.3	1.3 ± 1.2	0.1-6.8	39
Individualized (measured)**	6.7 ± 0.6 (7.0 ± 1.2)	5.4-9.0 (4.8-10.5)	0.9 ± 0.4 (1.2 ± 0.6)	0.5-1.9 (0.6-2.5)	90

Summarized from Lesar et al. 1982. JAMA 248: 1190-1193.

* Steady-state peak and trough serum concentrations were calculated for each dosing method in all (96) patients using pharmacokinetic parameters determined from serum concentration time data.

** Peak and trough serum concentrations measured (in 49 patients) 36 to 96 hours after initiation of the individualized dosage regimen.

patients using these pharmacokinetic parameters. Individualized pharmacokinetic method produce peak concentrations of 4 to 10 mg/L and troughs of 2 mg/L or less in significantly more patients (94%) than all predictive methods ($P < 0.01$). Furthermore, the predictive dosing methods did not produce concentrations necessary for more serious infections (peaks, 6 to 10 mg/L; and trough, < 2 mg/L) in the majority of patients (Table 9). In general, these predictive algorithms resulted in peak and trough serum concentrations in the therapeutic range in less than 50% of the patients compared with 90% with the individualized method. The investigators also demonstrated that the individualized method was a reliable technique for determining a patient's pharmacokinetic parameters and for predicting doses required to attain desired serum concentrations; there were no significant differences between the measured and predicted peak or trough concentrations (paired t test, $P > 0.1$). In conclusion, they suggested that the predictive dosing methods should be used for initiation of aminoglycoside therapy and then followed with measurement of serum concentrations and dosage adjustment by individualized method to ensure therapeutic concentrations early in the patient's treatment course.

Another study (Platt et al., 1982) compared the Sawchuk-Zaske indivilualization method (Sawchuk et al., 1977) with that of Hull and Sarubbi (1976), Chow et al. (1978) and a predictive algorithm of Tozer (1974). The method of Hull and Sarubbi has been previously discussed. The method of Chow et al. (1978) is able to predict serum drug concentrations from any dose based on a 1-

compartment linear pharmacokinetic model. This method assumes a volume of distribution of 0.28 L/kg and a normal half-life of 2 hours or it can vary half-life according to either actual or estimated creatinine clearance. The nomogram of Tozer (1974) modifies dosing based on the fraction of unchanged drug excreted in the urine and the fraction of functional creatinine clearance available in a particular patient. Table 10 shows the results of this comparison. Prediction error is the absolute value of the observed serum drug concentration minus the predicted value (Sheiner and Beal, 1981). Although measures of performance with the Sawchuk-Zaske method are considerably better than the others, there is still substantial variability among patients.

The dosing method of Sawchuk and Zaske (Sawchuk et al., 1977) has been tested in normal subjects (Zaske et al., 1980a, b, 1981; Sketris et al., 1981) and in various patient groups including burns (Zaske et al., 1976, 1982a), geriatric (Zaske et al., 1982c), surgical (Zaske et al., 1980a), obstetrical (Zaske et al., 1980b), gynecological (Zaske et al., 1981), obese (Sketris et al., 1981), and patients with Gram-negative infections and sepsis (Bootman et al., 1979; Lesar et al., 1982; Zaske et al., 1982b). Its ability to achieve and predict peak and trough gentamicin serum concentrations has been shown, for example, in 49 (Lesar et al., 1982) and 678 (Sawchuk et al., 1982b) patients studied (Table 11).

In a recent prospective study, Franson et al.(1988) have compared aminoglycoside (gentamicin, tobramycin) dosage regimens and subsequent serum concentrations in 30 patients treated initially

Table 10. Relationship of observed to predicted serum drug concentrations for 4 methods of gentamicin dosing.

Reference	Slope	Intercept	Correlation coefficient	Prediction error
Tozer (1974)				
Peak	0.43	2.71	0.38	1.07 ± 0.94
Trough	0.63	0.75	0.30	0.56 ± 0.71
Hull and Sarubbi (1976)				
Peak	0.36	2.73	0.38	1.30 ± 0.83
Trough	0.56	0.60	0.33	0.62 ± 0.58
Sawchuk et al. (1977)				
Peak	0.97	0.26	0.73	0.63 ± 0.66
Trough	1.26	-0.14	0.91	0.28 ± 0.35
Chow et al. (1978)				
Peak	0.49	2.37	0.53	0.94 ± 0.95
Trough	1.01	0.18	0.71	0.41 ± 0.52

from Platt et al. 1982. Clin. Pharm. 1: 361-365.

Table 11. Peak and trough serum concentrations achieved and predicted by the Sawchuk-Zaske dosing method

Reference	No. of patients studied	Serum concentration (mg/L) mean ± standard deviation	
		Peak	Trough
Lesar et al. (1982)	49		
measured		7.0 ± 1.2	1.2 ± 0.6
predicted		6.7 ± 0.6	0.9 ± 0.4
differences*		0.3 ± 1.2	0.3 ± 0.6
Zaske et al. (1982b)	678		
measured		6.9 ± 1.6	1.2 ± 0.7
predicted		6.9 ± 1.3	0.8 ± 0.6
differences*		-0.02 ± 1.6	0.3 ± 0.7

* Differences determined in each patient.

using traditional physician-determined methods and then switched to a pharmacokinetic-based treatment program. During the traditional prescribing phase, the physicians used any dosage regimen they felt was appropriate, but the information necessary to use Chan nomogram (1972) for calculating aminoglycoside dose and an instruction manual (including peak and trough information) were supplied. The exact process by which a particular dosage regimen was detemined was not known by the investigators. During this phase of treatment, which lasted 2 to 3 days, housestaff were required to obtain at least one set of blood samples for peak and trough concentrations. They had ample opportunity to alter the aminoglycoside dosages or dosage intervals according to their judgment. During the second (kinetic) phase, calculation of drug dosages and dosing intervals were based on serum concentration values, each patient's pharmacokinetic profile has been determined using a computer program (Schentag and Adelman, 1983). The investigators have found that patients received more drug during the kinetic phase (median 5 mg/kg) than during the traditional phase (median 3.6 mg/kg) and achieved greater peak serum concentration (5.9 versus 4.4 mcg/ml); 73% of kinetic peak values but only 27% of traditional peak values exceeded 5.0 mcg/ml; trough concentrations were comparable in both phases of study and no nephrotoxicity was observed. They have concluded that this pharmacokinetic-based management program achieved more consistently greater therapeutic peak concentrations and provided more individualized therapy than did physicians. Finally, these authors have suggested that the use of pharmacokinetic consultants might be of benefit in administering safely optimal aminoglycoside therapy.

Overall, it is clear that individualization of drug dosing by use of serum concentrations is a better method for achieving target serum gentamicin concentrations than are predictive algorithms.

4. Bayesian Method

Another aminoglycoside dosing method which uses measured serum drug concentration is a computerized Bayesian statistical approach (Perlin et al., 1981 quoted in Burton et al., 1985b; Jelliffe et al., 1983; Burton et al., 1984). This method uses routine clinical data in a predictive algorithm, then any number of serum drug concentrations to refine the prediction, thus allowing one to attain desired serum drug concentrations. Population pharmacokinetic values serve as the starting point and can be modified based on disease-related variables such as creatinine clearance, drug interactions, etc. The input of serum drug levels obtained in an individual patient then allows individualization of therapy by modifying estimates of the individual's pharmacokinetic parameters based on the variability of these parameters observed in the population. For example, volume of distribution and clearance of gentamicin for a patient with moderate renal insufficiency can be estimated from data in the literature assuming the patient behaves as the average. Based on the population derived estimate, a dosing regimen can be implemented. If a subsequently obtained serum drug concentration differs from that predicted, the patient clearly does not behave as average, and his pharmacokinetic parameters must be re-estimated to derive future dosing guidelines. In this simple case,

the patient may differ from average in terms of volume of distribution, in clearance, or in both. The Bayesian method assumes that the chances of a pharmacokinetic parameter being different in an individual are the same as the variability observed in the population. Consequently, if volume of distribution in the population is relatively constant with a small coefficient of variation, and clearance is more variable with a large coefficient of variation, the Bayesian re-estimation of the individual's pharmacokinetic parameters will modify clearance more than volume of distribution. In addition, this method allows weighting for variability in the assay, in sampling and dosing time, in compliance to outpatient therapy, and in giving the most recent serum drug concentration(s) the most weight. Thus, the Bayesian method is highly flexible and allows use of routinely obtained clinical and laboratory data; consequently, it is less labor-intensive than pharmacokinetic methods. Moreover, the Bayesian method is as accurate as any method yet developed.

Jelliffe et al. (1983) have reported in abstract form that this method is highly accurate, although insufficient data were presented in this preliminary report to comment on the findings. Burton et al. (1984) have compared a Bayesian method to physician intuition and to the Hull and Sarubbi nomogram (1977), and found the predictive algorithm to be more accurate and more precise than physician intuition and the Bayesian method to be better than both. For example, on average, physician dosing led to peak concentrations 2.6 mcg/ml lower and troughs 0.8 mcg/ml higher than desired

concentration; the predictive algorithm attained peaks 1.5 mcg/ml lower than desired concentration but reached the desired troughs; while the Bayesian method attain both desired peaks and troughs.

Gilman et al. (1986) found the Bayesian method to be as good a predictor of future serum gentamicin concentrations as nonlinear least-squares regression method. Godley et al. (1986) found similar predictive ability with 2 Bayesian programs, a nonlinear least-squares program and the Sawchuk-Zaske regression method. Neither group specified whether renal function was stable. Burton et al. (1986) also found no significant difference between the Bayesian and linear regression methods. All reports cited that the advantage of the Bayesian method was that it could be used with only 1 serum concentration. A similar lack of difference was found by Hurst et al. (1987) in 26 young, otherwise healthy patients with perforated (18 patients) or gangrenous (8 patients) appendicitis, remarkably uniform population parameter values and very stable renal function. In contrast to these findings, Chrystyn (1988) found that the Bayesian method predicted serum concentrations more precisely than the Sawchuk-Zaske method.

Administration

As mentioned in the previous chapter, intramuscular administration is avoided in critically ill patients because absorption is not complete in these patients. In general, the preferred route is intravenous administration.

Opinions vary on the optimum method for the intravenous administration of gentamicin. In the US, the manufacturers have recommended infusing a dose in 50 to 200 ml of saline or glucose solution over a period of 30 minutes to 2 hours. In the UK, some manufacturers recommend direct intravenous injection of a 2-ml dose over 2 to 3 minutes, while others recommend infusion with smaller volumes than in the US and shorter infusion times or recommend that gentamicin should not be given as a slow infusion at all (Reynolds, 1989).

Stratford et al. (1974) reported that concentrations of about 10 mcg/ml were obtained 5 minutes after administration of 80 mg or 1 mg/kg body weight of gentamicin given by intravenous injection over 2.5 to 3 minutes. However, Bailey and Lynn (1974) warned that toxic concentrations might be achieved as they had found that a similar rapid bolus injection had produced a peak serum concentration of 18.3 mcg/ml after 2.5 minutes falling to 9.3 mcg/ml at 10 minutes and 5.1 mcg/ml at 1 hour.

Subtherapeutic concentrations have been reported after the use of large-volume infusions of gentamicin and some consider (Elliott, 1985) that the use of infusions should be discouraged as they may also produce prolonged serum trough concentrations above 2 mcg/ml. However, Meunier et al. (1987) calculated that the pharmacokinetics and the peak serum concentration of gentamicin at equilibrium were similar after a slow bolus injection or an infusion over 15 minutes. They considered that infusion over 15 minutes would

avoid the large variations in peak serum concentrations obtained with longer infusion times.

Others have advocated rapid intravenous bolus injections rather than infusions for therapy of various infections, in order to produce high (though transient) serum peaks and thereby to augment the penetration gradient into various tissues (Korner, 1973). Although this approach appears to be safe (Korner, 1973; Mendelson et al., 1976), there is little evidence that it offers much pharmacological advantage (Kozak et al., 1977).

Although the manufacturers state that gentamicin is effective in CNS infections (including meningitis) caused by susceptible organisms, CSF concentrations of the drug following IM or IV administration are unpredictable and generally low. Gentamicin (without preservatives) is used intrathecally or intraventricularly to supplement IM or IV administration of the drug in the treatment of CNS infections (including meningitis and ventriculitis) caused by susceptible *Pseudomonas* (McEvoy, 1989).

In ophthalmologic use gentamicin has achieved therapeutic results when applied topically or by local injection (Appel and Neu, 1978). Topical use of the systemic aminoglycosides gentamicin, tobramycin or amikacin, should be discouraged because the widespread low level exposure will increase bacterial resistance (Schentag, 1980).