"Individualizing Aminoglycoside Therapy: Using Pharmacokinetic Principles as a Tool to Improve Patient Outcomes!"

Program Goals
1. To understand the critical importance of pharmacokinetic principles as a clinical tool for aminoglycoside antibiotics.
2. To define therapeutic endpoints for aminoglycoside antibiotics necessary to achieve desired patient outcome.
3. To understand and define therapeutic outcomes desired with aminoglycosides.

Educational Objectives
1. Describe and calculate the dosage regimen of an aminoglycoside antibiotic for a patient with Gram negative sepsis.
2. Define the half-life of an aminoglycoside when given serum concentration time data.
3. Calculate the distribution volume of an aminoglycoside in a patient when given serum concentration time data.
4. Describe the physiologic variables which will change the pharmacokinetic parameters of an aminoglycoside in a patient who has Gram negative sepsis.
5. Understand the clinical and pharmacokinetic reasons why aminoglycoside dosage regimens need to be individualized.
6. Describe the clinical importance of individualized dosage regimens have on patient outcomes.
7. Describe the most important time points when serum aminoglycoside samples should be obtained and used to determine pharmacokinetic parameters of half-life and distribution volume.
8. Describe the interpatient and the intrapatient variation with aminoglycosides and what clinical decisions can be applied to best ensure the desired patient outcome is attained.

Aminoglycoside Pharmacokinetics as a Clinical Tool to Improve Patient Outcomes

I. Introduction
A. Therapeutic use of aminoglycoside antibiotics.
B. Clinical response of patients who had life-threatening Gram negative sepsis.
C. Utilization of the tool for individualizing aminoglycoside regimens.
II. Defining the one compartment pharmacokinetic parameters for aminoglycoside antibiotics.

A. Half-life

Given serum concentration time data, be able to estimate the half-life in a specific patient. Be able to provide estimated time intervals to attain serum samples to quantitate the half-life.

1. Physiologic variables influencing or changing the half-life in a specific patient.

B. Distribution volume

Given serum concentration time data, be able to estimate the distribution volume in a specific patient. Be able to provide estimated time intervals to attain serum samples to quantitate the half-life.

The distribution volume ($V_d$) of the drug is then calculated using these estimates and the following equation, which considers the amount of drug eliminated during the infusion period:

$$V_d = \frac{K_o \left(1 - e^{-K_d t'}\right)}{K_d \left(C_{p_{max}} - (C_{p_{min}} e^{-K_d t'})\right)}$$

where $K_o$ is the rate of infusion (mg/h), $t'$ is the infusion period (h), $K_d$ is the drug’s elimination rate constant (hr$^{-1}$), $C_{p_{min}}$ is the predose serum concentration (ug/ml), and $C_{p_{max}}$ is the peak concentration. The infusion rate ($K_o$) is the dose (mg) administered over time (h).

1. Physiologic variables influencing or changing the distribution volume in a specific patient.

2. Physiologic compartments paralleling the distribution volume of aminoglycosides.

C. One compartment characteristics

1. One Compartment Model for Aminoglycosides

figure 1.
Distribution from central compartment to the tissue compartment is rapid in comparison to infusion rate ($K_0$) and under clinically normal conditions, the aminoglycoside antibiotics' serum concentration time relationship will resemble a one compartment model. These conditions include a one hour infusion ($K_0 = 100\text{mg}/60\text{min}$), relatively normal renal function ($\text{SCr} < 1.5 \text{mg\%}$), and normal state of hydration (extracellular fluid volume approximating 20% of body weight).

2. Clinical conditions where a Two Compartment Model is frequently observed.
   a. Rapid infusion rates ($> 1.5 \text{ mg/min}$)
   b. Abnormal renal function (in younger patients $\text{SCr} > 1.5 \text{ mg\%}$)
   c. Increased distribution volumes ($> 25\%$)
      i. Patients who are in CHF and have clinical evidence of edema.
      ii. Premature infants will have expanded ECF compartment.
      iii. Females immediately pre-partum or post-partum.
iv. Burn patients immediately post injury.

d. Reasons why a two compartment is difficult to use clinically.

i. Expensive

ii. Sampling strategy is difficult to anticipate.

iii. The mathematical model may not add anything to the one compartment model and clinical monitoring

e. Alternatives available clinically.

i. Minimize Error in one compartment model. Delay first sample after dose and prolong sampling period and use one compartment model.

ii. Altering dosage recommendation to reduce error.

III. Desired Therapeutic Endpoints

A. Patient selected peak concentrations

B. Patient selected trough concentrations

<table>
<thead>
<tr>
<th>table 1</th>
<th>SERUM CONCENTRATION GUIDELINES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gentamicin</td>
</tr>
<tr>
<td><strong>Peak</strong> (ug/ml)</td>
<td></td>
</tr>
<tr>
<td>Moderate--severe</td>
<td>6-8</td>
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<tr>
<td>Life threatening</td>
<td>8-10</td>
</tr>
<tr>
<td><strong>Trough</strong> (ug/ml)</td>
<td></td>
</tr>
<tr>
<td>Moderate--severe</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Life threatening</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

*Higher peak and trough serum concentrations may be safely utilized if clinical or bacteriologic data demonstrate the need.

C. Concentration endpoints are selected in each patient.

1. Patient's clinical condition
2. Type of infection and risk of mortality/morbidity

3. Suspected pathogen and antimicrobial sensitivity

IV Interpatient Variation

A. Half-life

1. Variation within patient groups.

The half-life of gentamicin and other aminoglycosides demonstrate substantial variation in a group of patients treated for sepsis. This variation occurs in patients who have normal renal function as determined by serum creatinine ($\leq 1.5$ mg/dl) or creatinine clearance ($> 100$ ml/min).

2. Effect of the interpatient of half-life on serum concentration time profile.

The short half-life of an aminoglycoside will result in subinhibitory serum concentrations within the first 1 to 2 hours of the dosing interval. This further defines the need of shorter dosing intervals in select patients who are hyperdynamic.

B. Distribution Volume

1. Variation within patient groups.

The distribution volume for gentamicin demonstrates substantial interpatient variability in a large group of patients initially treated for sepsis. This variation is similar for all aminoglycosides. During treatment, the variation is generally reduced because patients, who are initially dehydrated, have their fluid deficits replaced and patients, who are initially fluid overloaded, undergo diuresis and their fluid volumes return to normal values.

2. Effect of the interpatient of distribution volume on serum concentration time profile.

The interpatient variation in distribution volume can have an important effect on the serum concentration time profile for all aminoglycosides. Patients who are initially dehydrated and who have a small distribution volume will attain potentially toxic concentrations. If the same dose is administrated to a patient who is fluid overloaded and has a large distribution volume, the patient may not attain therapeutic serum concentrations.

V. Intrapatient Variation

A. Relationship of distribution volume and half-life

The relationship of gentamicin half-life and distribution volume is illustrated in 249 patients who had normal renal function. The larger the distribution volume caused a longer half-life of aminoglycoside. Alterations from normal values in the patient's aminoglycoside distribution volume and half-life are frequently observed in patients who have sepsis.

B. Effect of changes in distribution volume on half-life and on serum concentration time profile

The intrapatient variation in distribution volume can have an important effect on the serum concentration time profile for all aminoglycosides. The clearance of aminoglycosides will remain constant in many patients, but the distribution can change within a patient and will cause changes in the drug's half-life. This change is totally independent of a change in serum creatinine and is frequently observed clinically. A change in both dose and dosing interval may be necessary to achieve desired serum concentrations.
C. Effects of changes in the patient's hemodynamic state

1. Hyperdynamic to normal state or *vice versa*.

2. Hypodynamic to normal state or *vice versa*.

D. Changes in renal function

VI. Patient Factors Altering Pharmacokinetics of aminoglycosides.

1. Disease States:
   a. Renal Function

Patients who have compromised renal function have lower aminoglycoside elimination rates and more prolonged half-lives than patients who have normal renal function. The relationship between aminoglycoside elimination and estimates of renal function was originally established in healthy individuals. The variables involved were reported to be highly correlated. In patients with gram-negative sepsis, however, there is a marked decrease in the association of these variables. The half-life and elimination rate of these agents vary considerably for specific estimates of renal function. Only 35% of the variance (r²) in gentamicin elimination rate was explained by changes in creatinine clearance. In a report by Barza et. al, about 56% of the variance in gentamicin half-life could be explained by changes in serum creatinine. Similar relationship are also reported with tobramycin, sisomicin, netilmicin, and amikacin. Additionally, the association with measured creatinine clearance and predicted creatinine clearance was found to be very low.

b. Patients with ascites:

Patients who have ascites can have a markedly increased extracellular fluid compartment. These patients exhibit a large aminoglycoside distribution volume and a prolonged half-life. The distribution volume of gentamicin was determined by Gill and Kern in eight patients who had ascites. The distribution volumes in these patients were markedly increased, indicating the drug distributed into ascitic fluid. The large distribution volume reported in this study was substantiated in a recent study by Sampliner et. al. These investigators studied tobramycin pharmacokinetics in eight patients who had ascites secondary to alcoholic liver cirrhosis. The maximum concentration of tobramycin in ascitic fluid occurred at 4.4 ± 1.7 hrs after administration. In dosing patients who have severe hepatic disease, this third spacing phenomenon should be considered in estimating dosage requirements. A larger aminoglycoside dose must be given to these patients to ensure that desired peak concentrations will be achieved. These patients frequently require prolonged dosing intervals to prevent high trough concentrations. The prolonged half-life occurs even in those patients who have normal renal function. Additionally, the extracellular fluid compartment can change rapidly in these patients if effective diuretic therapy in instituted combined with fluid restriction. Aminoglycoside distribution volume and half-life can change rapidly in these patients during aminoglycoside therapy, and serum aminoglycoside concentrations must be carefully monitored to determine the necessary dosage adjustments.

c. Dialysis Patients

Clearance of all aminoglycoside agents during dialysis is similar. The amount of aminoglycoside removed during dialysis can vary considerably between and within patients. Blood and dialysate flow rates, duration of dialysis treatment, and type of dialyzer membrane are major factors that determine the amount of drug removed during hemodialysis. Clearance of the aminoglycoside is directly proportional to the flow rate. Septic patients may exhibit fluctuating flow rates because of hypotension and other changes occurring hemodynamically. The amount of drug dialyzed may also be influenced by the type of membrane in the dialyzer machine. Different membrane types can have different extraction efficiencies. Recently, Matzke et. al evaluated three different hemodialyzers and found their performance markedly different with respect to elimination and clearance characteristics of gentamicin and tobramycin. The amount of drug removed is directly proportional to the duration of dialysis. The longer the dialysis period, the greater the amount of drug removed.

d. Fever

Serum concentrations of gentamicin in humans and in animals are affected by elevations in body temperature. Febrile subjects demonstrated lower gentamicin serum concentrations than did afebrile patients. Lower aminoglycoside serum concentrations in febrile patients may result from increased drug clearance. In febrile patients,
the body's increased metabolic requirements can result in increased cardiac output, renal blood flow, and glomerular filtration. Thus, with increased renal perfusion and glomerular filtration, aminoglycoside clearance increases, resulting in lower serum concentrations.

e. Hematocrit

Barza et al reported a linear relationship between the reciprocal of the hematocrit and gentamicin half-life. As the hematocrit increased, the gentamicin half-life decreased. The reciprocal of the hematocrit explained 43% of the variance in the half-life. Gentamicin distribution volume has also been reported to relate statistically to hematocrit. Changing the extracellular fluid volume and intravascular volume has a direct effect on the hematocrit and explains the basis for the relationship between hematocrit and distribution volume. Changes in half-life are probably affected by the distribution volume and explain the relationship between hematocrit and half-life. These findings may be clinically important in estimating dosage and dosing intervals.

f. Age

Age is an important variable affecting aminoglycoside disposition, even when one accounts for the variation via renal function. There is a gradual decrease in elimination rate as the population ages. When the pharmacokinetic data are stratified according to age, the half-life of patients greater than 30 years of age is significantly longer than that occurring in younger patients. In burn patients less than 20 years old who had normal renal function, the mean gentamicin half-life was 1.1 hours compared to a mean half-life of 3.3 hours reported in older burn patients. The clearance of amikacin was significantly different in patients younger than 30 years of age (p < 0.001). The elimination rate and clearance of aminoglycosides continue to decrease within the geriatric population as age increases.

A number of physiologic processes change as the population ages, which may account for the substantial variation in aminoglycoside kinetic parameters among different age groups. With increasing age, there is decreasing proportion of total body water and/or muscle mass to the total body weight. Thus, aminoglycoside distribution volume will change, paralleling these changes in body water content. Additionally, aminoglycoside half-life may be a function of renal maturity. Elderly patients in general have prolonged aminoglycoside half-lives secondary to reduced kidney function. Age explains additional variance in elimination rate of aminoglycosides and appears to also affect other physiologic functions related to aminoglycoside disposition (i.e., cardiovascular function).

g. Geriatrics

In general, elderly patients have progressively decreasing renal function with increasing age; glomerular filtration rate and aminoglycoside clearance are also decreased with increasing age. These patients frequently require prolonged dosing intervals and lower daily dosages. Many geriatric patients who present to the hospital are clinically dehydrated and will require lower aminoglycoside doses to achieve desired peak serum concentrations. In contrast, elderly bedridden patients tend to have larger distribution volumes because many of these patients may have clinical signs or early signs of congestive failure. These patients frequently have underlying pathophysiologic processes that alter aminoglycoside disposition. The elderly patient who develops severe gram-negative sepsis may develop congestive heart failure at the same time. These patients will probably have an expanded distribution volume and substantially prolonged half-life secondary to increased extracellular fluid and edema. Aminoglycoside serum concentrations should be carefully monitored in these patients because of their greater susceptibility to toxicity.

h. Lean Body Weight

Lean body weight can affect aminoglycoside distribution volume and, therefore, drug disposition as well. Originally, it was thought that aminoglycosides distribute into lean body mass and not into excess weight or adipose tissue. However, pharmacokinetic studies indicate that aminoglycosides distribute into 5% or 6% of estimated excess weight. This closely approximates the extracellular fluid compartment of 8% to 10% that occurs in adipose tissue. Dosage estimates based on lean body weight could easily underestimate the dosage requirement of an obese patient. It is difficult to predict aminoglycoside requirements in obese patients without the benefit of serum concentration determinations.

i. Gender

Differences in aminoglycoside disposition have been associated with gender. Females reportedly have more rapid aminoglycoside half-lives and elimination rates than do males. This may be due to their smaller distribution volume in comparison to males. Females tend to have a lower proportion of muscle mass per kilogram body weight than do males. This significant relationship between elimination rate and gender was reported in 1,640 patients who received individualized gentamicin therapy. The relationship was significant even after the influence of age and weight were used as covariants.

j. Burn Patients

Burn patients have two distinct post-resuscitation phases in which aminoglycoside pharmacokinetic parameters can be substantially different. A wide variation in elimination rate, half-life, and distribution volume will occur in both phases. Aminoglycoside distribution volume is elevated during the initial phase of burn resuscitation and prior to the post-burn diuresis phase. This is especially true in those who develop gram-negative sepsis and in the elderly patients who may not diures the expanded fluid. The distribution volume in this phase frequently ranges from 0.3 to 0.5 L/kg or higher, and the half-life is excessively prolonged (five to seven hours). These patients require larger
doses and extended dosing intervals during this initial phase. After the diuretic phase, the distribution volume approaches the normal values of 0.15 to 0.2 L/kg, and the half-life decreases abruptly. These changes occur without parallel changes in creatinine clearance.

VII. Dosages Required to Attain Desired Serum Concentrations.

A. Interpatient Variation

The dosage requirements of gentamicin varied for 1,640 patients who had a normal serum creatinine. These requirements varied substantially in these patients.

B. Intrapatient Variation

The patient's dosage regimen will need adjustments during treatment to continually achieve therapeutic serum concentrations.

C. Dosage Interval Calculation

The patient's dosing interval (T) is calculated knowing the desired peak concentration (C_{p_{max}}), desired trough concentration (C_{p_{min}}), and infusion period (t'). The dosing interval can be calculated by:

\[ T = \frac{-1}{K_d} \ln \left( \frac{C_{p_{min}}}{C_{p_{max}}} \right) + t' \]

The calculated dosing interval should be rounded-off to a clinically convenient units such as 4, 6, 8, or 12 hours.

D. Dosage Calculation

The aminoglycoside infusion rate (Ko) in mg/hr is then calculated to achieve the desired serum concentrations. The following equation is used, which considers the amount of drug remaining from the previous dose and the amount eliminated during the infusion period:

\[ K_o = K_d V_d C_{p_{max}} \left( \frac{1 - e^{-K_d T}}{1 - e^{-K_d t'}} \right) \]

The infusion rate (mg/hr) is then calculated. The aminoglycoside dose is equal to the rate of infusion(Ko) times the length of infusion (t'). The dose is rounded-off to increments that can be conveniently prepared by pharmacy and administered by nursing.

VIII. Patient Outcomes Achieved.

A. Serum Peak and Trough Concentrations

Desired serum concentrations were achieved on the average for the patients treated. Continued patient monitoring and dosage adjustments are essential to ensure patient safety and therapeutic response.

B. Patient Response

1. Patient Survival
   a. Burn patient survival was increased.
   b. Burn patients who had ecthyma gangrenosum survived.
c. Patients who had Gram negative pneumonia's responded at a high rate.

2. Patient Safety

a. Nephrotoxicity appeared less frequently.

b. Overt ototoxicity, either vestibular or cochlear damage was not clinically apparent.

IX. Other Approaches to Dosing Aminoglycosides

*Initial Therapy:* Generally, similar initial dosage regimens are recommended for gentamicin, tobramycin, sisomicin, and netilmicin. The recommended initial dose for adult and geriatric patients are 1 to 2 mg/kg. Lower dosages (i.e., 1 mg/kg) should be utilized in the elderly patient who appears to be clinically dehydrated. In contrast, higher initial dosages (i.e., 2 mg/kg), but longer dosing intervals should be utilized in patients who have expanded extracellular fluid compartments such as the patient with congestive heart failure. Suggested initial dosage regimens for patients who have impaired renal function or hemodialysis patients are 1 to 2 mg/kg.

Similar initial dosage regimens are recommended for amikacin, kanamycin, and streptomycin. The recommended initial dose for adults are 5 to 7.5 mg/kg, regardless of the patient's renal function. In the treatment of urinary tract infections, a total dose of 10 mg/kg/d given in two or three divided doses is usually effective. Suggested initial dosage regimens for hemodialysis patients are 7.5 mg/kg and subsequent doses are 3.75 mg/kg after each dialysis. In selecting the initial aminoglycoside dose, the clinician should consider those factors reported to affect the aminoglycoside distribution volume. These factors include the patient's hydration status and the presence of edema. Overhydrated patients and those who have edema will have larger distribution volumes and require higher doses to achieve a desired peak concentration. For patients who are moderately to morbidly obese, lean body weight should be calculated to estimate the distribution volume of the drug. The severity of the infection should also be considered. These considerations will aid the clinician in selecting an initial dose at the upper or lower end of the dosing range.

Various dosing charts and nomograms have been proposed and are available to assist the clinician in estimating dosage requirements in patients who have normal or compromised renal function. These are based on statistical correlations between aminoglycoside elimination rate and estimates of renal function (usually serum creatinine or creatinine clearance). These relationships can have substantial error in predicting dosage requirements. Aminoglycoside dosage requirements can vary substantially from patient to patient, even in those who have normal renal function. Additionally, although patients who have abnormal renal function generally have reduced daily dosage requirements because of reduced aminoglycoside clearance, there is considerable overlap in dose and dosing interval requirements between patient groups. Aminoglycoside dosing charts and nomograms are initial guidelines only. These dosage regimens can produce substantial variations in serum aminoglycoside concentrations and should be subsequently adjusted based on serum concentration determinations and clinical response.

**Nomograms:** Several dosing methods for aminoglycosides have been published and are available to clinicians for predicting dosage requirements in patients who have normal or compromised renal function. These include the Sarubbi-Hull, "Rule of Eights", Dettli, Siersbaek-Nielsen and Chan methods. The predictability of these methods is low. This finding is due to a low association between drug elimination and renal function, a wide variation in distribution volume, and recently identified factors not previously included in the nomograms.

The method of Sarubbi-Hull utilizes serum creatinine, lean body weight, age and sex to predict creatinine clearance. For selected ranges of creatinine clearance, low, medium, and high dosage regimens are selected. This method allows the clinician to select different doses and dosing intervals for varying degrees of renal function and severity of infection. Of the several dosing methods available, this method considers more patient variables, which may improve estimates of glomerular filtration rate and aminoglycoside elimination.

The "Rule of Eights" method suggests a dose be administered at variable intervals depending on the patient's serum creatinine. Doses are given every eight hours for patients with normal serum creatinine. For patients who have abnormal renal function, the dosing interval is calculated by multiplying the patient's serum creatinine by a factor of eight and rounding the value to the nearest convenient intervals of 12, 18, 24, 36 or 48 hours. This approach can result in prolonged sub-inhibitory serum concentrations, especially in those who have severely compromised renal function. Additionally, this approach does not consider other factors recognized to influence aminoglycoside disposition.

The Dettli method utilizes estimates of lean body weight to determine the aminoglycoside distribution volume. The elimination rate constant is estimated from the patient's creatinine clearance. The following equation has been proposed:

\[ K_d = \text{CCr(cal)} \times 0.0024 + 0.01 \]

where \( K_d \) is the overall elimination rate constant, 0.0024 is the slope of the line, 0.01 is the y-intercept, and \( \text{CCr(cal)} \) is the estimated creatinine clearance.
is the patient's calculated creatinine clearance. The individual dosage regimen is then calculated from the estimated elimination rate constant. The clinician selects desired peak and trough serum concentrations and calculates a dosage regimen to achieve these. The clinician has the advantage of being able to select each patient's therapeutic endpoint.

The method of Siersbaek-Nielsen utilizes serum creatinine, lean body weight, and sex to estimate each patient's creatinine clearance. The distribution volume for all patients is assumed to be 0.26 L/kg of lean body weight. The lean body weight is estimated from Geigy's Scientific Tables, which utilizes the patient's age, sex, and height. This method suggests loading doses of 1.0 to 2.0 mg/kg of lean body weight, and the maintenance doses are determined as a percentage of the loading dose. The dosing intervals are determined for specific creatinine clearances. The aminoglycoside is administered every 8, 12, or 24 hours.

The dosing nomogram of Chan et al. utilizes a standard loading dose followed by a maintenance dose derived from a published nomogram. These maintenance doses are adjusted according to creatinine clearance estimates and the dosing interval is eight hours. Utilization of fixed dosing intervals can lead to substantial drug accumulation in patients who have compromised renal function.

Dosing methods derived from nomograms have several sources of errors and limitations. In general, these nomograms assume a constant distribution volume throughout the patient population and do not take into account the wide intrapatient and interpatient variation that has been reported. Nomograms use calculated rather than measured estimates of creatinine clearance rather than measured estimates of creatinine clearance which can represent an important source of error. In addition, several factors known to affect aminoglycoside disposition other than renal function, such as lean body weight, hemodynamic changes, and underlying disease states, are not considered in dosage nomograms.

Lesar et al. clinically evaluated four commonly used predictive dosing methods for gentamicin dosing. They compared the Sarubbi-Hull, Dettli, "Rule of Eights" and Chan methods with an individualized method in 96 consecutive septic patients. These four dosing methods were found to result in a large proportion of patients with subtherapeutic or potentially toxic serum concentrations. At times, toxic peak serum concentrations may occur concurrently with subtherapeutic trough values, or vice versa. Therapeutic serum concentrations (peaks of 6 to 10 \( \mu g/ml \), troughs of < 2 \( \mu g/ml \)) were achieved in 78\%, 43\%, 28\% and 39\% of patients who were dosed according to the four methods, respectively. A large number of these patients had long periods of subtherapeutic serum concentrations. The individualized method produced therapeutic serum concentrations in 90\% of patients.

**Book Chapters**


