Clinical Pharmacokinetics

Therapeutic Drug Monitoring of Antimicrobial Agents “Aminoglycosides”

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Introduction

• Pharmacokinetics (PK) is concerned with the time course of antimicrobial concentrations in the body,

• Pharmacodynamics (PD) is concerned with the relationship between those concentrations and the antimicrobial effect.

• Antibiotic dosing regimens have traditionally been determined by PK parameters only. However, PD plays an equal, if not more important, role.

• In this age of increasing antimicrobial resistance, PD becomes even more important because these parameters may be used to design dosing regimens which counteract or prevent resistance.
The primary measure of antibiotic activity is the minimum inhibitory concentration (MIC).
- The MIC is the lowest concentration of an antibiotic that completely inhibits the growth of a microorganism in vitro. While the MIC is a good indicator of the potency of an antibiotic, it indicates nothing about the time course of antimicrobial activity.

PK parameters quantify the serum level time course of an antibiotic. The PK parameters that are most important for evaluating antibiotic efficacy are:
- peak serum level (Cmax),
- trough level (Cmin),
- Area Under the serum concentration time Curve (AUC).
While these parameters quantify the serum level time course, they do not describe the killing activity of an antibiotic.

Integrating the PK parameters with the MIC gives us three PK/PD parameters which quantify the activity of an antibiotic:
- Peak/MIC ratio = Cmax divided by the MIC
- T>MIC = time above MIC is the percentage of a dosage interval in which the serum level exceeds the MIC
- 24h-AUC/MIC ratio = determined by dividing the 24-hour-AUC by the MIC.
Antimicrobial Patterns

• The three PD properties of antibiotics that best describe killing activity are:
  ▫ **time-dependence:** the length of time necessary to kill
  ▫ **concentration-dependence:** the effect of increasing concentrations
  ▫ **persistent effects:** include the Post-Antibiotic Effect (PAE). PAE is the persistent suppression of bacterial growth following antibiotic exposure

• Using these parameters, antibiotics can be divided into 3 categories:

<table>
<thead>
<tr>
<th>Pattern of Activity</th>
<th>Antibiotics</th>
<th>Goal of Therapy</th>
<th>PK/PD Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong>&lt;br&gt;Conc-dependent killing and Persistent effects</td>
<td>Aminoglycosides Daptomycin Fluoroquinolones Ketolides</td>
<td>Maximize concentrations</td>
<td>24h-AUC/MIC Peak/MIC</td>
</tr>
<tr>
<td><strong>Type II</strong>&lt;br&gt;Time-dependent killing and Minimal persistent effects</td>
<td>Carbapenems Cephalosporins Erythromycin Linezolid Penicillins</td>
<td>Maximize duration of exposure</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td><strong>Type III</strong>&lt;br&gt;Time-dependent killing and Moderate to prolonged persistent effects.</td>
<td>Azithromycin Clindamycin Oxazolidinones Tetracyclines Vancomycin</td>
<td>Maximize amount of drug</td>
<td>24h-AUC/MIC</td>
</tr>
</tbody>
</table>

Predictors of bacterial eradication

- **Aminoglycosides**
  - For aminoglycosides, it is best to have a Peak/MIC ratio of at least 8-10 to prevent resistance.
  - For fluoroquinolones vs gram negative bacteria, the optimal 24h-AUC/MIC ratio is approximately 125. Versus gram positives, 40 appears to be optimal.

- **Beta-lactams**
  - For beta-lactams and erythromycin, maximum killing is seen when the time above MIC is at least 70% of the dosing interval.

- **Azithromycin**
  - For vancomycin, a 24h-AUC/MIC ratio of at least 125 is necessary (some researchers recommend a ratio of 400 or more for problem bugs).
Aminoglycoside PD in vivo

PD of Beta-Lactams and Macrolides in Otitis Media

Vancomycin Outcome vs 24h-AUC/MIC

<table>
<thead>
<tr>
<th>24h-AUC/MIC</th>
<th>Satisfactory</th>
<th>Unsatisfactory</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 125</td>
<td>4 (50%)</td>
<td>4</td>
</tr>
<tr>
<td>&gt; 125</td>
<td>71 (97%)</td>
<td>2</td>
</tr>
</tbody>
</table>

Fluoroquinolone Pharmacodynamics vs S. pneumoniae

<table>
<thead>
<tr>
<th>24h-AUC/MIC ratio</th>
<th>Microbiological Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 33.7</td>
<td>(64%)</td>
</tr>
<tr>
<td>&gt; 33.7</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

Conclusion

- PK dosing has shown us that **one dose is not appropriate for all patients**.
- Pharmacodynamics shows us that **one target level is not appropriate for all patients**.
- We need to evaluate both the serum level data and the MIC, taking into consideration the PD properties of the drug.
- Numerous outcome studies have shown that class-appropriate PK/PD parameters are excellent predictors of antibiotic efficacy.
Aminoglycoside Antibiotics

Gentamicin
Tobramycin
Amikacin

Aminoglycoside antibiotics

- **bactericidal** antibiotics
- widely used for the treatment of severe **gram-negative** infections such as pneumonia or bacteremia, often in combination with a β-lactam antibiotic.
  - The MIC's of gram negative bacteria are usually less than 2 mcg/ml for gentamicin and tobramycin and 8 mcg/ml for amikacin.
- also used for **gram-positive** infections such as infective endocarditis in combination with penicillins when antibiotic synergy is required for optimal killing.
- Anaerobic bacteria are universally resistant because aminoglycoside transport into cells is oxygen-dependent.

- Have poor absorption from the gastrointestinal tract (highly water soluble and poorly lipid soluble compounds) → must be **administered parenterally** to achieve therapeutic concs in the systemic circulation → In most instances, they are administered by intermittent IV infusions.

- The three most commonly monitored aminoglycoside antibiotics are **gentamicin, tobramycin, and amikacin**
Adult doses

- The choice of an aminoglycoside dose is influenced by:
  - the specific agent,
  - infection (e.g., site and organism),
  - renal function,
  - weight or body composition of the patient.

- The usual dose for gentamicin and tobramycin is 5 to 7 mg/kg/day, administered over 30 to 60 minutes as a single daily dose or in divided doses every 8 to 12 hours;

- The dose of amikacin is 15 to 20 mg/kg/day, administered over 30 to 60 minutes as a single daily dose or in divided doses every 8 to 12 hours.

Pediatric doses

<table>
<thead>
<tr>
<th>Route</th>
<th>Age 0–4 Week Old</th>
<th>Age &lt;1 Week Old</th>
<th>Age 1 Week Old</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wt &lt;1200 g</td>
<td>Wt 1200–2000 g</td>
<td>Wt &gt;2000 g</td>
</tr>
<tr>
<td></td>
<td>Wt &lt;1200 g</td>
<td>Wt 1200–2000 g</td>
<td>Wt &gt;2000 g</td>
</tr>
<tr>
<td></td>
<td>Wt &lt;1200 g</td>
<td>Wt 1200–2000 g</td>
<td>Wt &gt;2000 g</td>
</tr>
<tr>
<td>Amikacin</td>
<td>IV, IM</td>
<td>7.5 mg/kg every 18–24 hours</td>
<td>7.5 mg/kg every 12 hours</td>
</tr>
<tr>
<td>Gentamicin or Tobramycin</td>
<td>IV, IM</td>
<td>2.5 mg/kg every 18–24 hours</td>
<td>2.5 mg/kg every 12 hours</td>
</tr>
</tbody>
</table>

Doses for infants and children are:
- amikacin 15–22.5 mg/kg/d IV or IM given every 8 hours,
- gentamicin or tobramycin 7.5 mg/kg/d IV or IM given every 8 hours.
Extended-interval aminoglycoside dosing can be conducted in pediatric patients.

After initial doses are started, steady-state aminoglycoside serum concentrations are used to individualize doses for either conventional or extended-interval dosing.
Pharmacodynamics of aminoglycosides

- Traditionally, aminoglycosides have been dosed multiple times a day.
- Investigations into the pharmacodynamic properties of aminoglycosides have yielded data that favor extended interval administration.
  - Bactericidal activity is concentration dependent
  - Concentration-dependent post-antibiotic effect
  - Saturable uptake mechanisms within the renal cortex and inner ear → extended interval dosing may also minimize the likelihood of developing nephrotoxicity and ototoxicity.

- This type of regimen is usually restricted to patients who have:
  - Reasonable renal function (e.g., ClCr > 60 mL/min)
  - Reasonably normal body composition (e.g., not excessively obese or having excessive third space fluid).

- Experience from RCTs suggests that once-daily administration of aminoglycosides results in similar efficacy and perhaps a decreased risk of developing toxicities when compared with traditional dosing.

Therapeutic and toxic plasma concs

Gentamicin and tobramycin
- **Extended interval dosing** (i.e., 5 to 7 mg/kg every 24 hours)
  - Peak plasma concs are in the range of 20 to 30 mg/L.
    - This peak conc target is based on the pharmacodynamic goal of achieving a peak to MIC ratio of greater than 10 and the breakpoint for susceptibility of 2 mg/L.
  - Trough concs are below the limit of detection by design to provide a drug-free interval, which reduces the risk for development of nephrotoxicity.

- **Traditional multiple daily dosing regimens**
  - Peak plasma concs are in the range of 5 to 8 mg/L.
    - Peak plasma concs < 2 to 4 mg/L are likely to be ineffective
    - Successful treatment of pneumonia may require peak concs of 8 mg/L or more.

Amikacin
- Peak concs are usually 20 to 30 mg/L;
- Trough concs are usually < 10 mg/L.
• Most available data correlating aminoglycoside concs with ototoxicity and nephrotoxicity refer to **trough plasma concs**,  
  ◦ Some data suggest a correlation between peak concs and toxicity.

• Gentamicin trough concs of **> 2 mg/L** have been associated with **renal toxicity**.  
  ◦ Note: the high trough concs may be the result, and not the cause, of renal dysfunction.  
  ◦ Fortunately, most patients who develop renal dysfunction during aminoglycoside therapy appear to regain normal renal function after the drug has been discontinued.

• **Ototoxicity** has been associated with trough plasma concs of gentamicin **> 4 mg/L for > than 10 days.**  
  ◦ When the trough conc is multiplied by the number of days of therapy, the risk of ototoxicity is increased when the product exceeds 40 mg/day/L.  
  ◦ Aminoglycoside ototoxicity also seems to be most prevalent in patients who have existing impaired renal function or have received large doses during the course of their treatment.

• The standard practice to use aminoglycoside plasma concs as predictors for both efficacy and toxicity.  
  ◦ Involves determining the individualized pharmacokinetic parameters based on measured peak and trough concs

• **One common question is whether aminoglycoside plasma concs should be monitored in patients receiving the drug once daily.**  
  ◦ In most cases, peak concs will have little meaning because they are likely to be well above the usual therapeutic range: ≈ 20 to 30 mg/L for gentamicin and tobramycin and about three times that value for amikacin.  
  ◦ Trough plasma concs do not appear to be useful in that they are likely to be well below the usual detectable range and may be misinterpreted due to the tissue redistribution (gamma phase).  
  ◦ In patients with diminished renal function, plasma level monitoring may be warranted to guard against excessive drug accumulation.
The adoption of once-daily aminoglycoside dosing at many institutions has led to less intensive monitoring of serum concs.

- Measuring the degree of drug exposure and peak conc (the peak AUC method of dosing)
  - a method of dosage individualization of extended interval aminoglycoside dosing based on a measured peak conc and an estimation of the AUC.
  - With this method, serum concs are obtained at a peak and approximately two to four half-lives later. The two levels are then used to calculate the 24-hour AUC and the extrapolated peak conc at 1 hour into the dosing interval.
  - The assumption with this method is that the level of drug exposure with extended interval dosing should be the same as conventional multiple daily dosing regimens
    - The target AUC$_{24}$ range for gentamicin and tobramycin is 70 to 100 mg.hr/L.

- Using a nomogram:
  - recommends that a single level be drawn 6 to 14 hours after the dose.
  - the nomogram then defines in graphical form whether the dosing interval is appropriate or needs to be extended.
  - Compared with the traditional method, this type of approach is much more simplified; however, it may not provide the same precise control of drug exposure [i.e., peak, area under the curve (AUC)] in patients who exhibit altered pharmacokinetics (i.e., third space fluid, burns, cystic fibrosis, spinal cord injury).

**Aminoglycoside pharmacokinetics**

occurs as antibiotic in the blood distributes into tissues, although drug is also cleared from the blood during this time, too. When infused over one hour, the distribution phase is usually not observed begins when blood and tissues are in near-equilibrium, and the predominate process is elimination from the body. The half-life for this phase of the curve is dramatically influenced by the patient’s renal function

occurs at very low serum concentrations (<0.5 mg/L) and represents the release of tissue-bound aminoglycoside into the blood where it will be cleared from the body. The gamma phase begins approximately sixteen hours post infusion.

Despite the existence of the three-compartment model for the aminoglycosides, pharmacokinetic calculations can be based on a one-compartment model that utilizes the second volume of distribution. The errors encountered when using a single-compartment model for aminoglycosides can be minimized if plasma drug concs are obtained at times that avoid the first and third distribution phases and at 24 hours after therapy has been initiated. Aminoglycoside concs < 1 mg/L should be evaluated cautiously because the influence of the large third compartment will become greater at these low concs.
Key PK parameters: Volume of distribution (Vd)

- The Vd of aminoglycosides is \(0.25 \text{ L/kg}\) (a wide range of 0.1 to 0.5 L/kg has been reported).
  - Aminoglycosides have low plasma protein binding and they cross membranes very poorly → their Vd is approximately equal to the extracellular fluid volume.

- **Obese patinets**
  - Since aminoglycosides distribute very poorly into adipose tissue, lean rather than total body weight (TBW) should result in a more accurate approximation of V in obese patients.
  - The aminoglycoside volume of distribution in obese subjects also could be adjusted based on the patient’s ideal body weight (IBW) plus 10% of his or her excess weight.
  - aminoglycoside antibiotics appear to distribute into extracellular space, and the extracellular fluid volume of adipose tissue is approximately 10% of adipose weight versus 25% which is an average for all the other tissues.

- **Patients with third space fluids:**
  - The volume of distribution of aminoglycosides is increased in patients with ascites, edema, or other enlarged “third space” volume.
  - One approach to approximating the increased volume of distribution for patients with ascites or edema is to increase the V by 1 L for each kg of weight gain.

- **Patients with cystic fibrosis** have a markedly increased Vd of 0.35 L/kg due to increases in extracellular fluid brought about by the disease process.
- **ICU patients** may have a Vd 25-50% above normal.
**Pediatric patients:**
- Pediatric patients < 5 years of age tend to have a larger Vd.
- Between birth and 5 years of age, the Vd probably continues to decline from an initial value of 0.5 L/kg to the adult value of 0.25 L/kg.

\[
\text{Aminoglycoside Vd (L) in Children 1 to 5 Years} = \left[0.5 \text{ L/kg} - \left(\frac{\text{Age in Years}}{5} \times 0.25\right)\right] \left(\frac{\text{Weight in kg}}{\text{Weight in kg}}\right) \quad [\text{Eq. 1.5}]
\]

*assumed that the child's weight in kg represents a weight that is not obese and does not contain significant excess 3rd space fluid.*

**Key PK parameters: Clearance (Cl)**
- The aminoglycoside antibiotics are eliminated almost entirely by the renal route.
- Since the aminoglycoside and creatinine clearances are similar over a wide range of renal function, aminoglycoside clearance can be estimated from the formulas used to estimate creatinine clearance when concs are within the therapeutic range.

\[
\begin{align*}
\text{Cl}_{\text{cr}} \text{ for Males (mL/min)} & = \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCR}_{\text{ser}})} \quad [\text{Eq. 1.6}] \\
\text{Cl}_{\text{cr}} \text{ for Females (mL/min)} & = \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCR}_{\text{ser}})} \\
& \times 0.85 \quad [\text{Eq. 1.7}]
\end{align*}
\]

*the age is in years, weight is in kg, serum creatinine is in mg/dL*

- Make sure you take into consideration adjustments for obesity and third spacing.
  - Generally, the IBW for obese subjects can be used;
  - adjustments for IBW in patients who are < 20% overweight are probably unnecessary.
  - In patients who are morbidly obese (i.e., actual body weight approximately double their IBW), use the non-obese (adjusted) weight
    Where: **Non-Obese Weight ≈ IBW + 0.4 (TBW - IBW)**
• **Non-Renal Clearance of aminoglycosides**
  - is \( \approx 0.0021 \text{ L/kg/hr} \) (or \( \approx 2.5 \text{ mL/min/70 kg} \))
  - is generally ignored in most patients, but it is significant in patients with diminished renal function

• In patients who are **functionally anephric** (0.3 L/hr or 5 mL/min) and receiving intermittent hemodialysis, a clearance value of \( \approx 0.0043 \text{ L/kg/hr} \) (5 mL/min/70 kg) represents the residual renal Cl and the non-renal Cl.
  - These values, however, are only approximations; serum concs of aminoglycosides should be monitored in patients with poor renal function.

• **Penicillin Interaction**
  - Carbenicillin, ticarcillin, and related extended-spectrum penicillins chemically inactivate gentamicin and tobramycin in vitro via formation of a covalent bond between the two antibiotic molecules
  - This inactivation can become **clinically significant in vivo in patients with renal failure**.
  - Although this interaction is usually not considered a route of aminoglycoside clearance, it does act as a mechanism for drug “elimination.”
  - **This interaction is a function of:**
    - the specific aminoglycoside,
    - In general, tobramycin and gentamicin interact with penicillins in a similar manner; amikacin is much less likely to interact with these penicillins.
    - the penicillin compound,
    - The newer semisynthetic acylureido penicillins appear to be less reactive than carbenicillin, and the cephalosporins appear to be relatively non-reactive.
    - the conc of the penicillin compound,
    - the temperature.
  - **For patients with very poor renal function who are receiving carbenicillin or ticarcillin, the additional gentamicin clearance can be approximated as follows:**

\[
\text{Tobramycin, Gentamicin Clearance by Carbenicillin or Ticarcillin (L/hr)} = \left(0.017 \text{ hr}^{-1}\right) \left(\frac{\text{Volume of Distribution for Aminoglycosides}}{\text{Volume of Distribution for Aminoglycosides}}\right) \text{[Eq. 1.8]}
\]

K of 0.017 hr\(^{-1}\) represents the in vitro elimination rate for aminoglycosides exposed to carbenicillin concs of 250 to 500 mg/L at a temperature of 37°C.
Key PK parameters: Elimination half-life

- **Half-life is a function of the Vd and Cl.**
- Since renal function varies considerably among individuals, the half-life is also variable.
  - Try to calculate the half-life of gentamicin in a 70-kg, 25-year-old man with a serum creatinine of 0.8 mg/dL and compare it to the drug’s half-life in a 75-year-old man with a similar Vd and a serum creatinine of 1.4 mg/dL.
- For this reason, the initial aminoglycoside dose and dosing interval should be selected with care.
- Although initial estimates of the patient’s aminoglycoside pharmacokinetic parameters may be highly variable, it is hoped that pharmacokinetic adjustments will optimize the achievement of therapeutic, yet nontoxic, concs of aminoglycoside antibiotics.

### KEY PARAMETERS: Aminoglycoside Antibiotics

<table>
<thead>
<tr>
<th>Therapeutic Serum Concentrations</th>
<th>Conventional dosing</th>
<th>“Once-daily” dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin, tobramycin</td>
<td>Peak 5–8 mg/L, Trough &lt; 2 mg/L</td>
<td>20 mg/L, Undetectable</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Peak 20–30 mg/L, Trough &lt; 10 mg/L</td>
<td>60 mg/L, Undetectable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>V&lt;sub&gt;a&lt;/sub&gt;</th>
<th>0.25 L/kg</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cl</th>
<th>Normal renal function (Cl&lt;sub&gt;Cr&lt;/sub&gt;) 0.0043 L/kg/hr 0.0021 L/kg/hr 1.8 L/hr</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>AUC&lt;sub&gt;24&lt;/sub&gt;</th>
<th>70–100 mg × hr/L</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>t&lt;sub&gt;1/2&lt;/sub&gt;</th>
<th>Normal renal function 2–3 hr Functionally anephric patients 30–60 hr</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>fu (fraction unbound in plasma)</th>
<th>&gt; 0.95</th>
</tr>
</thead>
</table>

<sup>a</sup>Volume of distribution should be adjusted for obesity and/or alterations in extracellular fluid status.

<sup>b</sup>A functionally anephric patient is a dialysis patient with kidneys intact. A surgically anephric patient is a dialysis patient with kidneys removed. Hemodialysis clearance of 1.8 L/hr refers to low-flux hemodialysis, not high-flux or peritoneal dialysis.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Half-Life</th>
<th>Vd</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult, normal renal function</td>
<td>2 hours</td>
<td>0.26 L/kg</td>
<td>Usual doses 3–5 mg/kg/d for gentamicin, tobramycin, netilmicin, or 15 mg/kg/d for amikacin when using conventional dosing. Usual doses are 5–7 mg/kg/d for gentamicin or tobramycin using extended-interval dosing.</td>
</tr>
<tr>
<td>Adult, renal failure</td>
<td>50 hours</td>
<td>0.26 L/kg</td>
<td>Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
<tr>
<td>Burns</td>
<td>1.5 hours</td>
<td>0.26 L/kg</td>
<td>Burn patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
<tr>
<td>Penicillin therapy (patients with creatinine clearance &lt;30 mL/min)</td>
<td>Variable</td>
<td>0.26 L/kg</td>
<td>Some penicillins (penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can bind and inactivate aminoglycosides <em>in vivo</em> or <em>in vitro</em> (e.g., lab test tubes).</td>
</tr>
<tr>
<td>Obesity (&gt;30% over IBW) with normal renal function</td>
<td>2–3 hours</td>
<td>V (in L) = 0.26 [IBW + 0.4 (TBW – IBW)]</td>
<td>Aminoglycosides enter the extracellular fluid contained in adipose tissue requiring a correction factor to estimate volume of distribution.</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>1.5 hours</td>
<td>0.35 L/kg</td>
<td>Larger volume of distribution and shorter half-life usually results in larger daily doses.</td>
</tr>
<tr>
<td>Acites/overhydration</td>
<td>Variable</td>
<td>V (in L) = (0.26 · DBW) + (TBW – DBW)</td>
<td>Aminoglycosides distribute to excess extracellular fluid; correction equation assumes that weight gain is due to fluid accumulation. Alterations in volume of distribution can cause secondary changes in half-life.</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>3–4 hours</td>
<td>0.26 L/kg</td>
<td>While receiving hemodialysis, aminoglycoside half-life will decreases from ~50 hours to ~4 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>36 hours</td>
<td>0.26 L/kg</td>
<td>While receiving peritoneal dialysis, ~36 hours. Renal failure patients commonly have fluid imbalances that may decrease (underhydration) or increase (overhydration) the volume of distribution and secondarily change half-life.</td>
</tr>
</tbody>
</table>

### Time to sample

- Correct timing of the sample collection is important because aminoglycoside antibiotics have a relatively short half-life and a small but significant distribution phase.
- The most widely accepted guidelines recommend that:
  - samples for **peak serum concs** should be obtained 1 hour after the maintenance dose has been initiated.
    - This recommendation assumes that the drug is infused over about 30 minutes; an acceptable range for the infusion period is 20 to 40 minutes. If it is longer than 40 minutes, peak concs should be obtained ≈ 30 minutes after the end of the infusion to ensure that distribution is complete.
    - Others have suggested that peak measurements should be obtained later in the dosing interval to avoid the distribution phase, particularly with extended interval dosing due to the potential dose-dependent distribution phase.
  - **Trough concs** generally should be obtained within the half-hour before the administration of the next maintenance dose.
    - In cases in which the trough concs are expected to be lower than the assay sensitivity (particularly with extended interval dosing), an earlier sampling time may be appropriate so that measurable trough concs can be obtained and patient specific pharmacokinetic parameters derived.
- Ideally, the **interval between the two conc measurements** should be two to four half-lives to provide more precise estimates of the half-life and reduce the potential for the later conc to fall below the level of assay sensitivity. In all cases, the exact time of sampling and dose administration should be recorded.
Concentration/time plot for gentamicin 120 mg given as a $\frac{1}{2}$-hour infusion (squares with solid line) and as a 1-hour infusion (circles with dashed line).

When given as a $\frac{1}{2}$-hour infusion, end of infusion concentrations are higher because the serum and tissues are not in equilibrium. A $\frac{1}{2}$-hour waiting time for aminoglycoside distribution to tissues is allowed before peak concentrations are measured. If aminoglycosides are given as 1-hour infusions, distribution has an opportunity to occur during the infusion time, and peak concentrations can be obtained immediately. In either case, concentrations 1 hour after the infusion was initiated are similar.

- When aminoglycoside plasma concs are sampled at a time that extends beyond the expected peak, it is possible to **back-extrapolate** the plasma conc to the “clinical peak,” which is 1 hour after the start of the infusion.
  - The “clinical peak” conc has generally been used as a guide to aminoglycoside efficacy.

\[
C = C^0 e^{-kt}
\]

\[
C^0 = \frac{C}{e^{-kt}}
\]

- The standard of practice in many institutions has been to **obtain the first aminoglycoside samples after three or four doses of aminoglycoside have been administered**. The majority of patients will be approaching steady state by this time;
  - however, with the wide availability of computers and pharmacokinetic software programs, it is not absolutely necessary to wait until steady state is achieved. With extended interval dosing, there should be no significant accumulation with multiple dosing; therefore, measurements can be obtained after any dose.
  - reasonable pharmacokinetic parameters can be estimated using a one-compartment model and two plasma samples in most cases.
• **Peak and trough conc (bolus model vs. infusion model)**
  - To evaluate whether the IV bolus dose model is appropriate, the duration of infusion (one-half hour) should be compared to the apparent drug half-life.
    - When the duration of infusion or absorption is **less than one-sixth of the half-life**, then the **bolus dose model** can be used.
    - If, however, the duration of drug input is **greater than one-sixth of the half-life**, then an **infusion model** should be used.

### bolus model

$$C_1 = \frac{(S)(F)(\text{Loading Dose})}{V} (e^{-kT_1})$$

$$C_{ss1} = \frac{V}{(1 - e^{-kT_1})} e^{-kT_1}$$

### infusion model

$$C_2 = \frac{(S)(F)(\text{Dose/t}_{in})}{Cl} (1 - e^{-kT_{in}})(e^{-kT_2})$$

$$C_{ss2} = \frac{Cl}{(1 - e^{-kT_1})} \frac{(1 - e^{-kT_{in}})}{(1 - e^{-kT_1})(e^{-kT_2})}$$

---

**Graphic representation of a drug administered as a bolus (—) or as a short infusion (- - -) and (......).**

- The bolus dose model assumes that drug input or absorption is instantaneous. The decay interval, $t_1$ (i.e., $t_{in} + t_2$), is therefore assumed to begin at the start of the infusion.
- In contrast, the infusion model assumes that the decay interval ($t_2$) begins at the conclusion of the infusion period ($t_{in}$).
- When $t_{in}$ is ≤ 1/6 of a $t^{1/2}$ (......), the concs are approximately the same for the short infusion and bolus dose model.
- When $t_{in}$ is considerably > 1/6 of a $t^{1/2}$ (- - -), the concs calculated by the short infusion and bolus dose model are substantially different.
Intermittent intravenous infusion at steady state. The infusion is administered over $t_{in}$ hours, and $\tau$ is the dosing interval; $t_2$ represents the time from the end of the infusion to the time of sampling.

**Question #1**

- R.W. is a 30-year-old, 70-kg, non-obese woman with a serum creatinine of 0.9 mg/dL. An initial gentamicin dose of 140 mg was infused intravenously over 30 minutes.
  1. Calculate the plasma conc of gentamicin 1 hour after the infusion was started (i.e., one-half hour after the infusion was completed).
  2. If R.W. was given 140 mg of gentamicin over one-half hour every 8 hours. Predict her peak and trough plasma concs at steady state.
  3. If R.W. was given tobramycin 7 mg/kg QD, what would be the calculated steady-state peak conc 1 hour after starting the half-hour infusion? Also predict subsequent steady-state plasma concs 12 hours after starting the infusion and at the trough.

Note: Use the bolus model and the infusion input model in your calculations and explain the differences in the answers.
### Intramuscular Administration

- When aminoglycosides are given intramuscularly they exhibit very good bioavailability of ~100% and are rapidly absorbed with maximal concentrations occurring about 1 hour after injection.
  - A peak plasma conc should be obtained 1 hour after the IM dose is administered.

- Exceptions to this situation are patients who are hypotensive or obese.
  - **Hypotensive patients** shunt blood flow away from peripheral tissues, such as muscle, to provide maximal blood flow to internal organs. As a result, intramuscularly administered drugs may be malabsorbed in hypotensive patients, such as those with gram-negative sepsis.
  - Care must be taken with **obese individuals** to use a long enough needle to penetrate subcutaneous fat and enter muscle tissue when administering aminoglycoside antibiotics. Drug injected into poorly perfused fatty tissue will likely be malabsorbed.

### Dosing methods

- Achieving therapeutic serum levels of aminoglycosides early in the course of treatment is critical to therapeutic success.
- Dosing error on the high side is preferable to the risks of under-treatment.
- An adequate loading dose is critical for rapid attainment of therapeutic peak levels.
- Dosage regimens necessary to achieve therapeutic aminoglycoside serum concentrations can be quantitatively determined by using simple pharmacokinetic principles. Individualized pharmacokinetic parameters are determined from the patient's serum concentration versus time data.
Hull and Sarubbi Nomogram Method

- For patients who do not have disease states or conditions that alter volume of distribution, the only two patient-specific factors that change when using the pharmacokinetic dosing method is patient weight and creatinine clearance.
- It is possible to make a simple nomogram to handle uncomplicated patients with a standard volume of distribution.
- The Hull and Sarubbi aminoglycoside dosing nomogram is a quick and efficient way to apply pharmacokinetic dosing concepts without using pharmacokinetic equations.
- With a simple modification, it can also be used for obese patients.

For details about this nomogram:
Refer to Applied Clinical Pharmacokinetics (Chapter 4)

The Hull and Sarubbi aminoglycoside dosage nomogram is based on this dosage-calculation method and includes precalculated doses and dosage intervals for a variety of creatinine clearance values.

The nomogram assumes that $V = 0.26 \text{ L/kg}$ and should not be used to compute doses for disease states with altered $V$.
Pharmacokinetic Formulas

Initial Dosing:
- based solely on the population model
- **Determine dosing weight (DW)**
  \[ DW = LBW + ((ABW - LBW) \times CF) \]
  where ABW = actual weight
  CF is a correction factor for obesity, **usually 40%**, but literature values vary:
  - Amikacin = 38%
  - Gentamicin = 43%
  - Kanamycin = no correction
  - Netilmicin = 50%
  - Tobramycin = 58%
- **Determine loading dose (LD)**
  - Gentamicin, Tobramycin, Netilmicin: LD = 2mg/kg DW
  - Amikacin & Kanamycin: LD = 7.5mg/kg DW
- **Determine maintenance dose (MD)**
  - **Estimate elimination rate (Kel)**
    \[ Kel = 0.01 + (\text{CrCl} \times 0.0024) \]
  - **Estimate Volume of distribution (Vd)**
    \[ Vd = 0.27 \text{ L/kg} \times \text{DW} \]
  - **Calculate ideal maintenance dose (IMD)**
    \[ IMD = Kel \times Vd \times Cptmax \times (1 - e^{-Kel \times \tau} / (1 - e^{-Kel \times t_{inf}})) \]
  - **Select practical dosage and interval**
  - **Calculate expected peak & trough levels**
    \[ \text{Peak} = (MD / t_{inf} \times Vd \times Kel) \times (1 - e^{-Kel \times t_{inf}} / (1 - e^{-Kel \times \tau})\] 
    \[ \text{Trough} = \text{Peak} \times e^{-Kel \times (\tau - t_{inf})} \]
    where \( t_{inf} \) = length of infusion
Adjusting maintenance dose using Sawchuk and Zaske's method

- Patient specific pharmacokinetic parameters are calculated using the proven pharmacokinetic method of Sawchuk and Zaske.

- **Determine elimination rate (Kel)**
  \[ Kel = \frac{(\ln (C_{\text{max}}/C_{\text{min}}))}{\text{time between samples}} \]
  where \( C_{\text{max}} = \) Peak level
  \( C_{\text{min}}' = \) Trough after dose

- **Determine Volume of distribution (Vd)**
  \[ VD = \frac{[(\text{Dose}/t_{\text{inf}}) / (\text{kel})] x (1 - e^{-\text{kel} \times t_{\text{inf}}})}{C_{\text{max}} - (C_{\text{min}} x e^{-\text{kel} \times t'})} \]
  where \( C_{\text{max}} = \) Peak level
  \( C_{\text{min}} = \) Trough level before the dose
  \( t' = \) hours between time \( C_{\text{min}} \) drawn and end of infusion

- **Determine ideal dosing interval (tau)**
  \[ \tau = t_{\text{inf}} + (-1 / \text{kel}) \times \ln (C_{\text{max}}/C_{\text{min}}) \]
  where \( C_{\text{min}} = \) Target trough
  \( C_{\text{max}} = \) Target peak

- **Determine ideal maintenance dose (IMD)**
  \[ \text{IMD} = \text{Kel} \times Vd \times C_{\text{max}} \times (1 - e^{-\text{Kel} \times \tau} / 1 - e^{-\text{Kel} \times t_{\text{inf}}}) \]

- **Select practical dosage and interval**

- **Calculate expected peak & trough levels**
  \[ C_{\text{pss max}} = \frac{(\text{MD} / t_{\text{inf}} \times Vd \times \text{Kel}) \times (1 - e^{-\text{Kel} \times \tau} / 1 - e^{-\text{Kel} \times t_{\text{inf}}})}{1} \]
  \[ C_{\text{pss min}} = \text{Peak} \times e^{-\text{Kel} \times (\tau - t_{\text{inf}})} \]

Adjusting maintenance dose using Bayesian 1-compartment model

- Minimize Bayesian function

- The Bayesian method uses population-derived pharmacokinetic parameters (ie., Ve and Kel) as a starting point and then adjusts those parameters based on the serum level results, taking into consideration the variability of the population-derived parameters and the variability of the drug assay procedure. To achieve that end, the least squares method based on the Bayesian algorithm estimates the parameters which minimize the following function:

\[ SS = \sum_{i=1}^{n} \left( C_{i} - f(t_{i}, P) \right)^2 / \sigma_i^2 + \sum_{j=1}^{m} \left( \bar{E}_j - \bar{P}_j \right)^2 / \omega_j^2 \]

- **Determine ideal dosing interval (tau)**
  Same as Sawchuk and Zaske's method

- **Determine ideal maintenance dose**
  Same as Sawchuk and Zaske's method

- **Select practical dosage and interval**

- **Calculate expected peak & trough levels**
  Same as Sawchuk and Zaske’s method
Hartford Nomogram Method for Extended-Interval Dosing

- The dose in this nomogram is **7 mg/kg (dosing weight)** targets a **peak conc of 20 to 30 mg/L**

- **Determine interval**
  - The dosing interval is adjusted based on the degree of renal function in order to maintain the target peak conc and also achieve a drug-free interval of ≈ 6 hours to reduce accumulation within the renal cortex and inner ear.

<table>
<thead>
<tr>
<th>Creatine Clearance</th>
<th>Initial Dose and Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 mL/min</td>
<td>7 mg/kg every 24 hr</td>
</tr>
<tr>
<td>40–60 mL/min</td>
<td>7 mg/kg every 36 hr</td>
</tr>
<tr>
<td>20–40 mL/min</td>
<td>7 mg/kg every 48 hr</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>7 mg/kg, then follow levels to determine time of next dose (level &lt; 1 mcg/mL)</td>
</tr>
</tbody>
</table>

The three interval break points on the **Hartford interval adjustment nomogram** are the approximate decay curves from a 7mg/kg gentamicin dose. These decay curves were calculated using a one compartment model with a volume of distribution of 0.25 L/kg and an elimination rate calculated from creatinine clearances of 25, 40, and 60 ml/min for 48, 36, and 24 hour intervals respectively. To use the Hartford nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of two.

- Gentamicin or tobramycin concs obtained 6 to 16 hours following a 7mg/kg dose are plotted on the nomogram relative to the time of sampling following the dose.
- **Three regions** are defined in the nomogram corresponding to the appropriate dosing interval that should be chosen based on the single measured conc.
- concs that fall within the Q24h quadrant indicate that the dosing interval of 24 hours should be maintained. concs that fall in the Q36h or Q48h quadrant indicate that the dosing interval should be extended to 36 or 48 hours.
- Example: if a patient was initiated on a dose of 7 mg/kg every 24 hours and had a measured conc of 8.2 mg/L ≈ 9 hours after the dose, the nomogram indicates that the dosing interval should be extended to every 36 hours.
- It is important to note that the Hartford interval adjustment nomogram is only valid for a 7mg/kg dose.

- A nomogram for the less aggressive dose of 5mg/kg was developed by a consensus panel.

- The consensus panel argues that the 48 hour interval should be abandoned and that patients with a CrCl less than 40ml/min should be dosed by traditional pharmacokinetic methods.

- To use the consensus nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of three.

- The consensus panel also suggests that younger patients with excellent renal function may require Q 12 hour dosing.

- A 5mg/kg dosing algorithm for this subpopulation has been proposed by Urban and Craig.

- To use the Urban and Craig nomogram for 15mg/kg doses of amikacin, multiply the drug-level scale by a factor of three.

- Some have questioned the validity of all ODA nomograms because they are based on one-compartment parameters derived from traditional dosing methods. Some pk studies have shown that the pharmacokinetics of aminoglycosides at high doses differ significantly from those at traditional doses. Therefore, it is argued that nomograms based on an assumption of similar kinetics are invalid.
Computer programs

- A number of computer programs are available to help clinicians dose aminoglycosides and other therapeutic agents.
- Computers tend to be more flexible than nomograms in that the user often can select dosing intervals and peak or trough concs based on clinical judgment. In addition, they enable dosage determination based on data (including multiple sets of measurements) obtained under non-steady-state conditions, which is particularly important in patients with changing renal function.
- Bayesian analysis has been incorporated into most computerized pharmacokinetic programs and has been proven to provide very precise estimates of the pharmacokinetic parameters.
- One potential pitfall, however, is that the user must be familiar with the algorithms initially used to define expected pharmacokinetic parameters and how patient-specific parameters are revised when plasma concs and dosing histories are supplied.
- In the revision process, the user must be able to recognize data that are obviously wrong and to interpret the computer output to ensure that the parameters and dosing recommendations are reasonable.
- The computer should be viewed as a labor-saving device, not as a substitute for a thorough understanding of the pharmacokinetic process.

Useful equations

\[ K = \frac{\ln \left( \frac{C_1}{C_2} \right)}{t} \]

\[ V = \frac{(S)(F)(Dose)}{C_{ss1}} \left( \frac{e^{-kt_1}}{1 - e^{-kT}} \right) \]

\[ CI = (K)(V) \]

\[ \text{Dose} = \frac{(C_{ss1})(V)(1 - e^{-kT})}{(S)(F)(e^{-kt_1})} \]

\[ t/2 = \frac{(0.693)(V)}{CI} \]

\[ \text{AUC}_{24} = \frac{(\text{Dose in mg})(24 \text{ hr})/t}{\text{Cl in L/hr}} \]

\[ \text{AUC}_{24} \text{ New} = \frac{(\text{Dose Old})}{\text{AUC}_{24} \text{ Old}} \]

\[ V = \frac{\text{Dose}}{(C_{\text{peak}} - C_{\text{min}})} \]

\[ \text{Cl} = \frac{(S)(F)(Dose/t_{\text{in}})}{C_{ss2}} \left( \frac{1 - e^{-kt_1}}{(1 - e^{-kT})} \right) \left( e^{-kt_1} \right) \]
Question #2

- Y.B., a 70-kg, 38-year-old patient with a serum creatinine of 1.8 mg/dL, has been receiving IV tobramycin, 100 mg over one half hour every 8 hours, for several days. A peak plasma conc obtained 1 hour after the start of an infusion was 8 mg/L, and a trough conc obtained just before the initiation of a dose was 3 mg/L.

1. Estimate the apparent elimination rate constant \((K)\), clearance \((Cl)\), and volume of distribution \((V)\) for tobramycin in Y.B.

2. The microbiology report reveals *Pseudomonas aeruginosa* with an MIC of 1 mcg/mL. Calculate a dosing regimen for Y.B. that will achieve a peak conc of > 10 mg/L (peak:MIC > 10:1) and a AUC24 in the range of 70 to 100 mg.hr/L.

Question #3

- C.I. is a 50-year-old, 60-kg man with a serum creatinine of 1.5 mg/dL, who is receiving 350 mg of amikacin IV over one-half hour every 8 hours at midnight, 8:00 a.m., and 4:00 p.m. He had a trough conc of 6 mg/L obtained just before the 8:00 a.m. dose, and a peak conc of 15 mg/L obtained at 9:00 a.m.

1. Assuming these peak and trough concs represent steady-state levels, calculate C.I.'s elimination rate constant, clearance, and volume of distribution.

2. Evaluate whether these parameters seem reasonable and should be used to adjust C.I.'s amikacin maintenance dose.
D.H., a 40-year-old man, was admitted to the hospital following an automobile accident. He is 5 feet 5 inches tall and on admission weighed 85 kg. He was taken for abdominal surgery and postoperatively became hypotensive and required large volumes of fluid to maintain his blood pressure. Currently, he weighs 105 kg and has a serum creatinine of 2 mg/dL. D.H. is to receive gentamicin empirically after his abdominal surgery.

1. Estimate his pharmacokinetic parameters
2. Estimate the required gentamicin dose to achieve peak gentamicin concs > 10 mg/L and an AUC\textsubscript{24} between 70 and 100 mg.hr/L.
Question #5

• D.L., a 38-year-old, 70-kg patient with renal failure, is receiving gentamicin and ticarcillin for treatment of a fever of unknown origin.
1. How might the concurrent administration of ticarcillin influence the pharmacokinetics of gentamicin?
2. Are there other antibiotic combinations that may influence gentamicin dosing?

Question #6

• D.W., a 20-year-old, 60-kg man, is receiving 80 mg of tobramycin infused IV over a 30-minute period every 8 hours. His serum creatinine has increased from 1 to 2 mg/dL over the past 24 hours. Because his renal function appears to be decreasing, three plasma samples were obtained to monitor serum gentamicin concs as follows: just before a dose, 1 hour after that same dose, and 8 hours after that dose (two troughs and one peak level). The serum gentamicin concs at these times were 4, 8, and 5 mg/L, respectively.
1. Calculate the volume of distribution, elimination rate constant, and clearance of tobramycin for D.W.
2. Using the pharmacokinetic parameters calculated for D.W., develop a dosing regimen that will produce reasonable peak and trough concs of tobramycin.
• Troughs are not the same → tobramycin is accumulating
• Steady state eq. should not be used
• Estimate a revised value for k and then t_{1/2}
• You can use the bolus model
• The dose and the change in conc can be used to calculate V_d
• Cl can then be calculated

**Figure 5-11** If a patient has not received enough doses to be at steady state, or doses have been given on an irregular schedule, the minimum concentration (C_{min}), maximum concentration (C_{max}), and an additional postdose concentration (C_3) can be used to compute clearance, volume of distribution, and half-life.
Question #7

- M.S., a 70-kg non-obese female, undergoes 4 hours of hemodialysis every 48 hours. She is functionally (not surgically) anephric, and gentamicin is to be started.

1. Calculate a dosing regimen that achieves a peak conc of 6 mg/L and then maintains average levels of 3.5 mg/L.
   - The reported clearance for aminoglycosides in functionally anephric patients is \( \approx 0.0043 \text{ L/kg/hr} \), and aminoglycoside clearance by low-flux hemodialysis is 20 to 40 mL/min, with an average value of \( \approx 30 \text{ mL/min} \).
   - 2 approaches:
     - giving daily and postdialysis doses.
     - administer the aminoglycoside only after dialysis.

2. How would the above situation have differed if peritoneal dialysis rather than hemodialysis had been used?
   - The usual clearance value is 4 ml/min/m\(^2\) with an average value of 5-10 ml/min for a 70 kg patient
   - The total amount of drug removed during the dialysis may be as much as 30% or more
   - Doses can be given IV or intraperitoneally

Question #8

- A patient with meningitis is being considered for treatment with intrathecal (IT) or intraventricular gentamicin.

1. Which of these routes is preferred and what pharmacokinetic parameters are expected?
Question #9

- T.C. is receiving tobramycin 360 mg IV over one-half hour every 24 hours at 9:00 a.m. Levels drawn at 11:00 a.m. and 9:00 p.m. were 15.0 mg/L and 0.9 mg/L, respectively.

1. Calculate the peak conc expected at 10:00 a.m., or 1 hour after starting the 9:00 a.m. tobramycin infusion, and the AUC\textsubscript{24} to determine the appropriateness of the current dosing regimen.

Question #10

- O.L., a 52-year-old man in the critical care unit with multiple organ failure, is receiving CRRT with a total output of 2 L/hr (ultrafiltration and dialysis flow rate of 1 L/hr each). His current weight is 65 kg (up from 60 kg 2 days ago) and his serum creatinine is 2.8 mg/dL. Pending cultures he is to be started on tobramycin.

1. What would be a reasonable starting dose for O.L.?