



## **Pharmacokinetic Training Packet for Pharmacists**

Compiled by Elizabeth D. Hermsen, Pharm.D., M.B.A.  
Thanks to Erin Iselin, Scott McMullen, and Chris Shaffer for your help  
reviewing the packet!!!

Any questions? Call or email Elizabeth at 559-4287/ehersmen@nebraskamed.com

## Table of Contents

Pharmacokinetic definitions and principles	3
Aminoglycoside overview	4
Once daily aminoglycoside dosing	8
Aminoglycoside pharmacokinetic calculations	10
Vancomycin overview	13
Vancomycin pharmacokinetic calculations	16
Clinical Pearls	18
General – Aminoglycosides and Vancomycin	18
Dosing of Aminoglycosides in Cystic Fibrosis	18
Clinical Pharmacokinetic Consult Service	19

## Pharmacokinetic Definitions and Principles

### Kel, Ke, or Kd or Elimination Rate Constant

- The fraction or percentage of the total amount of drug in the body eliminated per unit of time.<sup>1</sup>
- Estimated with 2 drug levels taken between doses (the slope of the line). To be accurate, 2-4 half-lives should occur between the levels.<sup>1</sup>
- In pharmacokinetic calculations, the term  $e^{-k_{el}(t)}$  represents the fraction of the serum concentration that remains. Thus,  $1 - e^{-k_{el}(t)}$  represents the fraction of the serum concentration that is eliminated.

### $t_{1/2}$ or Half-life

- The time required for the TOTAL amount of remaining drug in the body to decline by 50%.<sup>1</sup>
- Sometimes referred to as  $\beta t_{1/2}$  to distinguish it from the distribution half-life,  $\alpha t_{1/2}$ , used in two compartment modeling.<sup>1</sup>

### Peak, $C_{max}$ <sup>1</sup>

- $C_{max}$  is the maximum measurable drug concentration at the end of an infusion BEFORE significant distribution occurs.
- The peak is the measured drug concentration AFTER distribution.

### Vd or Volume of Distribution<sup>1</sup>

- The volume of distribution is the theoretical size of the compartment necessary to account for the total drug amount in the body if it were present throughout the body in the same concentration found in the plasma.
- Factors that may effect the volume of distribution include; protein binding, hydration, lean body mass, third spacing, burns, nutrition, fever, sepsis, disease states, drug-drug interactions, etc.

### Creatinine Clearance – CrCl

- The renal glomerular filtration rate (GFR) is estimated by determining the CrCl.<sup>2</sup>
- Examination of the Cockcroft-Gault equation reveals that serum creatinine values less than 1 mg/dl will greatly elevate the calculated creatinine clearance. This is especially true for elderly patients, malnourished patients, and spinal cord injury patients. These populations have reduced muscle mass as a fraction of total body weight and so may generate less creatinine. It has been recommended in these populations to round the serum creatinine value up to 1 mg/dl.<sup>3</sup>

# Aminoglycoside Overview

## Background

The aminoglycoside antibiotics – gentamicin, tobramycin, amikacin, netilmicin, streptomycin, and neomycin – contain amino sugars in glycoside linkage. They are rapidly bactericidal. The primary intracellular site of action of aminoglycosides is the 30S ribosomal subunit. Aminoglycosides disrupt the normal cycle of ribosomal function by interfering with the first step of protein synthesis.<sup>4</sup>

Aminoglycosides are concentration dependent antibiotics, meaning that as aminoglycoside concentration increases, the rate and extent of bacterial killing increases. Presently, investigators suggest optimizing the aminoglycoside peak serum concentration to bacterial MIC ratio (Peak/MIC) to a value  $\geq 10:1$ .

Bacterial killing is thought to occur in a biphasic fashion. Initially, bacteria are killed at an extremely rapid pace in a concentration-dependent fashion. After approximately two hours and a 3 log kill (99.99% killing), the rate of bacterial killing slows. This phenomenon is thought to be due to adaptive resistance or through a down regulation of aminoglycoside transport into the bacteria through energy dependent transport processes.

While the post antibiotics effect (PAE) is generally thought to increase with concentration dependent antibiotics, this may not be the case with aminoglycosides. Limited data suggest that the PAE in gram negative bacteria may wane over time with multiple doses of aminoglycoside.

## Routes of Administration

- IV, IM, IH, topical cream or ointment, and ophthalmic

## Pharmacokinetic Parameters

**Table 1: Key Parameters for Aminoglycoside Antibiotics**

Therapeutic Serum Concentrations		
Gentamicin, tobramycin	<i>Conventional dosing</i> <sup>1</sup> Peak 4-10 mcg/mL Trough < 2 mcg/mL	<i>Once-daily dosing</i> <sup>5,6</sup> Peak 20 mcg/mL Trough - undetectable
Amikacin	<i>Conventional dosing</i> <sup>1</sup> Peak 15-40 mcg/mL Trough <5- 10 mcg/mL	<i>Once-daily dosing</i> Peak 40- 60 mcg/mL Trough -undetectable
<b>Volume of distribution</b> <sup>1</sup>	0.25 L/kg (0.1-0.5 L/KG) 0.5 L/kg (children < 5 yrs)	-
<b>Half-life</b> <sup>4</sup>	0.5-3 hr – normal renal function 30-60 hr – anephric patients	-

- Absorption<sup>2</sup>
  - Aminoglycosides are highly polar cations and are very poorly absorbed from the intestinal tract.
  - IM – peak concentrations 30-60 minutes post-dose.
  - IV (given over 30-60 minutes) – peak concentrations 30-60 minutes post-infusion.
- Distribution
  - Aminoglycosides are poorly distributed into the CNS.<sup>4</sup>
  - There is negligible binding to plasma albumin.<sup>4</sup>
  - The volume of distribution of aminoglycosides approximates the volume of extracellular fluid. In normal volunteers, this comprises about 20 to 35% of their body weight. However, the percent of body weight attributed to extracellular fluid changes with physiologic conditions. For example, dehydration associated with gram-negative sepsis results in an extracellular fluid compartment that is less than 20 percent of body weight. Newborn infants have a large extracellular fluid volume for their weight. Thus, their

distribution often approximates 50 percent of their body weight. Obese patients, because of the excess contribution of adipose tissue to the body weight but not to the overall distribution volume, will have a normal value of 10 to 20% of their body weight. In patients with ascites, edema, or other enlarged “third space”, the volume of distribution is increased. To estimate the volume of distribution of patients with ascites or edema one approach is to increase the volume of distribution by 1 L for each kg of fluid weight gain.<sup>1</sup>

Any situation resulting in a distribution volume of > 35% for a patient at lean body weight or > 20% for an obese patient should be thoroughly investigated for both biologic and artifactual causes. Once Vd is determined for a specific patient, it may still change during the course of therapy.

- Aminoglycosides distribute very poorly into adipose tissue.<sup>1</sup>
- Elimination<sup>4</sup>
  - Excreted almost entirely by glomerular filtration (85-95%).
  - The t<sub>1/2</sub> of aminoglycosides is between 0.5-3 hours with normal renal function
  - Aminoglycosides are removed by hemodialysis and, to a lesser extent, by peritoneal dialysis.

### Indications and Spectrum of Activity

- Aminoglycosides are indicated in the treatment of bacterial neonatal sepsis, bacterial sepsis, urinary tract infections, respiratory tract infections, gastrointestinal tract infections (including peritonitis), skin infections, bone infections, and soft tissue infections.
- **Gram Negative Infections** – Aminoglycoside antibiotics are useful for gram negative infections. The primary pathogens they are used to treat include:  
Enterobacteriaceae:

*Escherichia coli*  
*Proteus spp.*  
*Enterobacter spp.*  
*Acinetobacter spp.*  
*Citrobacter spp.*  
*Morganella spp.*  
*Serratia spp. (S. marcescens)*  
*Klebsiella spp.*  
*Pseudomonas aeruginosa*

Tobramycin is more active than gentamicin by one or two MIC tube dilutions against *Pseudomonas aeruginosa*. Gentamicin is more active by one or two MIC tube dilutions against *Serratia marcescens*. Amikacin is often held in reserve to treat resistant pathogens that develop during therapy. Other aerobic gram-negative bacilli (*Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Haemophilus influenzae*) are susceptible but are rarely treated with aminoglycosides.

- **Gram Positive Infections** – Aminoglycosides have activity against some gram positive isolates but are not considered primary agents. Enterococcal infections may be treated with a combination including penicillin, ampicillin, or vancomycin. Aminoglycosides may also be used as adjunctive therapy for Staphylococcal infections. Lastly, aminoglycosides may be used in combination with a cell wall active agent for various streptococcal infections (usually seen in *S. viridans* endocarditis). Data suggest penetration is the issue with streptococci, as is the case with enterococci.

#### Enterococci:

Enterococci are intrinsically resilient to aminoglycosides with MIC's > 500 mcg/mL. The primary problem is the ability of the aminoglycoside to get into the bacterial organism. Use of a cell wall active agent such as penicillin G, ampicillin, or vancomycin, in combination, will break down the cell wall, allowing the aminoglycoside to enter the bacteria. Generally, the combination of a beta-lactam antibiotic or vancomycin with either gentamicin or streptomycin is considered to be synergistic in killing the bacterial organism. If aminoglycosides are to be used, current

recommendations suggest peak gentamicin concentrations of 3 to 5 mcg/mL for gentamicin and 20 mcg/mL for streptomycin. Presently there is very little data to suggest a beneficial role for once-daily dosing in the management of enterococcal infections.

Enterococci are considered clinically resistant if their MIC is > 2000 mcg/mL. In this situation not only is there the problem of antibiotic penetration but also the enterococci have likely acquired (through a plasmid) the ability to enzymatically inactivate the aminoglycoside. There are approximately 5 aminoglycoside inactivating enzymes that are of clinical importance. Fortunately, when enterococci are gentamicin resistant, they are generally streptomycin susceptible and vice versa. This however is not the situation with tobramycin or amikacin which are not usually recommended as adjunct therapy for enterococcal infections.

Staphylococci:

The value of aminoglycosides as adjunctive therapy for staphylococci has been extensively questioned in the literature. Data suggest that the addition of an aminoglycoside to nafcillin therapy shortens the duration of bacteremia by about one-half day. No beneficial effect has been shown for a reduction in mortality. Despite these data, aminoglycosides are used by many clinicians in this situation. If an aminoglycoside is to be used, the clinician should recognize that extending aminoglycoside therapy beyond five days may place the patient at risk of aminoglycoside toxicity. Thus far, peak gentamicin concentrations of 3 to 5 mcg/mL seem adequate for adjunctive therapy. Very little data is available to suggest a meaningful role for once-daily dosing in staphylococcal infections being primarily managed with either vancomycin or a beta-lactam antibiotic.

- **Anaerobic Infections** – Anaerobes are intrinsically resistant to aminoglycosides.

**Toxicity/ Side Effects**

- The two most concerning problems are ototoxicity and nephrotoxicity; both reportedly occur in approximately < 2 to 10% of patients. Auditory toxicity is generally a bilateral high frequency loss that generally will not greatly affect most patients' lifestyle but will likely be a permanent effect. Vestibular toxicity is perhaps the most severe form of aminoglycoside toxicity because it permanently affects the patients' ability to balance.
- Aminoglycosides rarely cause neuromuscular blockade.

**Laboratory Monitoring of Therapy**

**Table 2: Serum Concentration Sampling Times for Traditional and Extended-Interval Dosing of Aminoglycosides**

	<b>Peak Sample Time</b>	<b>Trough Sample Time</b>	<b>Hospital Cost</b>	<b>Comments</b>
Traditional Dosing <sup>1</sup>	1 hour post IM injection 30 Min post 30-60 min infusion	≤ 30 min before dose (IM and IVPB)	G: \$10.43 T: \$13.75 A: \$15.78	Obtain levels after 3-4 doses (after ~5 half-lives). Most patients should be at steady-state at this time.
Extended Interval (once-daily) Dosing <sup>5,6</sup>	Not indicated.	Not indicated	G: \$10.43 T: \$13.75 A: \$15.78	Obtain random level 10-12 hours after dose given. No significant accumulation with multiple dosing; therefore, levels can be obtained after the first dose.

## Dosing

Traditionally, tobramycin or gentamicin have been dosed 80mg every 8 hours or 1.5-2.5 mg/kg every 8 hours. At The Nebraska Medical Center, we attempt to individualize the aminoglycoside dose and dosage interval specific to individual patients using population pharmacokinetics. Additionally, once daily aminoglycoside dosing (ODA) is advocated when appropriate, which uses daily doses ranging from 4 to 7 mg/kg/day. This approach is designed to produce higher peak concentrations than seen with conventional or individualized dosing strategies and thus increase the Cp-max/MIC ratio. The use of the 24 hour dosing interval is designed to create an "aminoglycoside-free" period during the dosage interval. It is believed that this period will reduce accumulation of aminoglycosides in tissues such as the inner ear and kidney and will thus reduce drug-related toxicity. The "aminoglycoside-free" period should also assist in overcoming adaptive resistance. The optimal timeframe for this period is presently unknown.

One large aminoglycoside dose given once daily rather than several divided doses given on multiple occasions through the day may result in less net transfer of aminoglycoside from the blood into the tissue. This is believed to be accomplished by saturating the rate by which the aminoglycoside is moved into the tissue. Smaller but more frequent doses are not believed to saturate drug transport into the tissue and ultimately produce higher tissue concentrations than ODA. Thus, between saturation of the amount of aminoglycoside moving into the tissue and the use of an "aminoglycoside free" period, ODA strategies should be less toxic to the patient through a reduction in aminoglycoside tissue accumulation.

At this time, there appears to be at least three schools of thought regarding the appropriate dosing of aminoglycosides: traditional, individualized, and ODA.

## Once Daily Aminoglycoside Dosing or Extended-Interval Dosing <sup>5,6</sup>

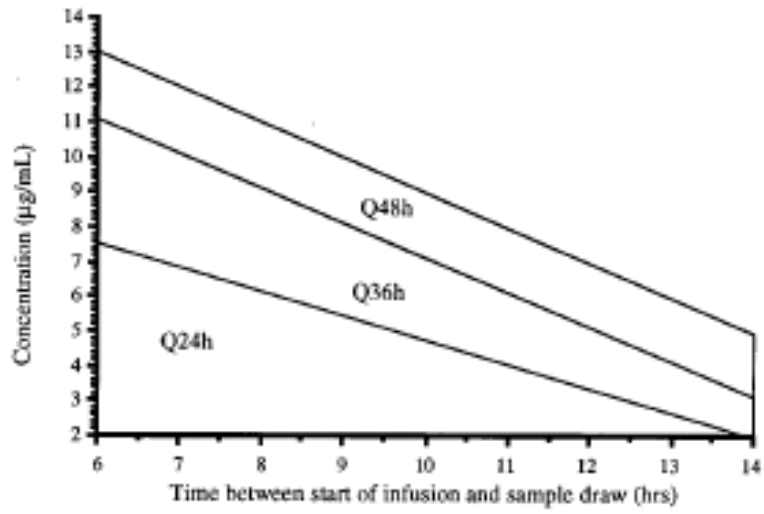
- The theories behind ODA include:
  - Aminoglycosides have concentration dependent activity. The rate of bacterial killing increases as drug concentration is increased. As stated previously, investigators suggest optimizing the aminoglycoside peak serum concentration to bacterial MIC ratio (Peak/MIC) to a value  $\geq 10:1$  to maximize bacterial killing.
  - The combination of a high peak and an “aminoglycoside-free” interval will help to reduce the selection and the emergence of resistant organisms (by eliminating the adaptive resistance phenomena), and minimize aminoglycoside-associated toxicity.
  - A high peak concentration of aminoglycosides leads to a longer duration of post-antibiotic effect (PAE).
- Exclusion criteria - pregnancy, breastfeeding, burns (>20%), ascites, cystic fibrosis, cirrhosis, dialysis, solid organ transplants, neutropenia, endocarditis, and CrCl < 20 mL/min. PLEASE NOTE: Once daily dosing should be considered in all patients for which an aminoglycoside is ordered for a suspected or documented Gram-negative rod infection, except for those that meet the exclusion criteria.
- Dosing
  - Use Actual body weight (ABW)
  - If patient is obese (>20% over ideal body weight - IBW) use dosing body weight (DBW)
$$DBW = IBW + [0.4 (ABW - IBW)]$$
  - Tobramycin/ gentamicin - dose at 4 to 7 mg/kg
  - Amikacin – dose at 15 mg/kg

**Table 3: Extended-Interval Aminoglycoside Dosing**

Estimated CrCl (mL/min)	Initial Dosing Interval
> 60 mL/min	Q24H
40-59 mL/min	Q36H
20-39 mL/min	Q48H
< 20 mL/min	Not recommended

- Therapeutic monitoring and dose adjustment
  - Levels should be obtained only in the following situations:
    - Random serum level 10-12 hours **AFTER THE START** of the infusion of the first dose to confirm appropriate serum level.
    - Confirm an appropriate serum concentration after dosage adjustment.
    - Suspected toxicity (oto- or nephro-) or when there is a change in or impaired renal function while on maintenance therapy.
    - Reaffirm a seriously abnormal or unusual serum concentration (i.e., potential line draws, inappropriate times, etc.)
    - Weekly monitoring of prolonged therapy with aminoglycosides
  - Dosage adjustments should be made according to the Hartford Nomogram (Figure 1).
    - **Important Notes:**
      - Because the Hartford Nomogram was based on a dose of 7mg/kg, if a lower dose is being used, the resultant level should be multiplied by a factor equal to 7 mg divided by the dose used. Example: If a patient is receiving 5mg/kg/day and the 10h post-dose level was 2 mcg/mL, you would multiply the level by 1.4 (7/5) to give a level of 2.8 mcg/mL. This adjusted level is the one you would plot on the Hartford nomogram.
      - If using amikacin, plot ½ of the serum concentration on the nomogram.
    - If the level falls on the line, choose the longer interval for administration.
    - If the aminoglycoside level falls off the nomogram, traditional dosing should be used.

Figure 1. Hartford Nomogram



## Aminoglycoside Pharmacokinetic Calculations – Traditional Dosing

### Guidelines for Aminoglycoside Serum Levels for Individualized Dosing (not ODA)

Levels should be obtained according to the following guidelines:

- A. Patient not responding to therapy as expected.
- B. Suspected toxicity (oto- or nephro-) or patient has a change in or impaired renal function while on maintenance therapy.
- C. Reaffirm a seriously abnormal or unusual serum concentration (i.e., potential line draws, inappropriate times, etc.)
- D. To determine that a therapeutic level has been achieved after culture results have been reported and the decision to continue the aminoglycoside has been made.
- E. Initial dosage check for prophylactic or empiric therapy in neutropenic patients or suspected *Pseudomonas* infections (i.e., cystic fibrosis or ventilator-dependent patients).
- F. Weekly monitoring of prolonged therapy with aminoglycosides.

### Definitions

IBW	=	ideal body weight
ABW	=	actual body weight
DBW	=	dosing body weight
kel	=	elimination rate constant
Vd	=	volume of distribution
$\tau$	=	dosing interval
t	=	time of infusion
t <sub>before</sub>	=	time between blood draw and start of infusion
t <sub>end</sub>	=	time from end of infusion to blood draw
t <sub>1/2</sub>	=	half-life
C <sub>max</sub>	=	peak serum level at steady-state
C <sub>min</sub>	=	trough serum level at steady-state
SCr	=	serum creatinine

### Empiric Dosing – No Levels

$$1. \text{ CrCl} = \frac{(140 - \text{age}) \times \text{IBW} (\times 0.85 \text{ if female})}{72 \times \text{SCr}}$$

#### Ideal Body Weight (IBW)

Males: 50 kg + 2.3 kg per inch > 60 inches  
 Females: 45.5 kg + 2.3 kg per inch > 60 inches

2. Use population kinetics to calculate a dosing regimen (see Pharmacokinetic Pocket Card and use "empiric" formulas). Use DBW = IBW + [0.4(ABW – IBW)] if patient ABW >20% over IBW.

### Individualized Dosing (levels obtained) – Calculate patient-specific kel and Vd

$$1. \text{ kel} = \frac{\ln(C_{\text{max}}/C_{\text{min}})}{\tau - (t + t_{\text{end}} + t_{\text{before}})}$$

$$2. \text{ Cmax}_{\text{actual}} = \frac{C_{\text{max}}}{e^{-\text{kel}(t_{\text{end}})}}$$

3. See Pharmacokinetic Pocket Card for specific Vd formulas under "After levels."

4. If you want to adjust the dose, plug patient-specific kel and Vd into dose equations and verify appropriate levels with the equations for estimated peak and trough at steady state.

**Desired Levels for Various Infections**

<b>Medical Condition</b>	<b>Desired Peak</b>	<b>Desired Trough</b>
<b><i>Gentamicin/ Tobramycin</i></b>		
Synergy (Gram-positives)	3-5	<1
UTI, endometriosis, pyelonephritis	4-6	<1
Tissue Infections, pneumonia, sepsis*	6-8	<2
Cystic Fibrosis	10-12	<1
<b><i>Amikacin</i></b>		
Moderate Infections	15-25	<5
Severe Infections	25-40	<10

\*For more severe infections, such as pneumonia or sepsis, we usually recommend pushing the peak more towards 8 mcg/mL due to penetration issues and better outcomes shown with higher peaks.

## References for Aminoglycosides

1. Winter ME. Basic Clinical Pharmacokinetics Fourth Edition. Lippincott Williams & Wilkins. Philadelphia. 2004; 19,131-171, 451-76.
2. Dipiro JT, Spruill WJ, Blouin RA, Pruemer JM. Concepts in Clinical Pharmacokinetics, third edition. American Society of Health-System Pharmacists. Bethesda, MD 2002. Pages 49, 189-232.
3. DiPiro JT, Talbert RL, Yee GC, et al. Pharmacotherapy; a pathophysiologic approach, fifth edition. McGraw-Hill Medical Publishing Division. New York, New York 1999. Pages 33-54.
4. Micromedex® Healthcare Series. Thompson Vol 123. Exp 3/2005.
5. Nicolau DP, Freeman CD, Belliveau PP, et.al. Experience with once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents and Chemother 1995;39(3):650-5.
6. Ferriols-Lisart R, Alós-Alimiñana M. Effectiveness and safety of once-daily aminoglycosides: a meta-analysis. Am J Health-Syst Pharm 1996;53:1141-50.

# Vancomycin Overview

## Background

Vancomycin is a tricyclic glycopeptide antibiotic that exhibits bactericidal activity by blockage of the glycopeptide polymerization in the bacterial cell wall. This produces an immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.<sup>1</sup> Vancomycin is considered to be a concentration-independent or time-dependent killer of bacteria. Therefore, increasing antibiotic concentrations beyond the therapeutic threshold will not result in faster killing or eliminate a larger portion of the bacterial population. Vancomycin is indicated for the treatment of severe staphylococcal infections (including methicillin-resistant staphylococci), endocarditis (including staphylococcal, streptococcal, diphtheroid), and in the treatment of pseudomembranous colitis caused by *C. difficile* (given orally only).<sup>2</sup>

Vancomycin is also utilized for infections caused by penicillin-susceptible pathogens in patients who are penicillin-allergic. Several studies have shown that with both staphylococci and enterococci, vancomycin does not kill the bacteria as quickly or sterilize the blood as rapidly as nafcillin/oxacillin or ampicillin, respectively. For this reason, many authors suggest that unless the patient has an allergy to beta-lactams or has a methicillin-resistant staphylococcal infection, the patient would be better served using a beta-lactam agent rather than vancomycin.

Concern over the increasing problems with vancomycin resistant enterococci (VRE) prompted the Center for Disease Control to issue a statement suggesting appropriate prescribing criteria for vancomycin (MMWR 44:No RR-12, September 22, 1994). Vancomycin is not recommended for:

- Routine surgical prophylaxis
- Treatment of a single positive blood culture for coagulase-negative staphylococci
- Empiric therapy of a febrile neutropenic patient where no evidence of gram-positive infection exists
- Continued empiric therapy
- Selective gut decontamination
- MRSA colonization
- Primary therapy for pseudomembranous colitis
- Topical application or irrigation
- Treatment of MSSA or other susceptible gram-positive infections in dialysis patients
- Prophylaxis in CAPD patients
- Prophylaxis in low birth weight infants
- Systemic or local prophylaxis for indwelling central or local catheters

## Pharmacokinetic Parameters<sup>1,3</sup>

Absorption – Oral absorption is negligible, however it does seem to concentrate in the colon (for treatment of *C. difficile*).

Distribution – Widely distributed into body tissues except CSF. Penetration into the CSF is enhanced with inflamed meninges (e.g., meningitis). Volume of distribution = 0.7 L/kg and does not significantly change for most disease states or conditions.

Elimination – When given IV, primarily excreted via kidneys. Oral doses are excreted primarily in the feces. Clearance = 0.65 X CrCl. Elimination half-life = 4-6 hrs in those with normal renal function. This is prolonged in patients with varying degrees of renal insufficiency.

Therapeutic Plasma Concentrations – peak = 25-40 mcg/mL, trough = 5-15 mcg/mL

## Concentration-toxicity Relationship

Shortly following the release of vancomycin to the market in 1956, reports began to surface describing ototoxicity secondary to vancomycin therapy, with serum concentrations ranging from 80-100 mcg/mL.<sup>4</sup> Based on this, the authors recommended therapeutic drug monitoring of vancomycin to reduce the risk of ototoxicity. This side effect, however, has been seen in only 2% of patients who receive vancomycin. Cantu and colleagues performed a literature search that yielded 53 reported cases of ototoxicity over a 30-year period.<sup>5</sup> Of these cases, only 17 were patients using

monotherapy, all of which were reversible. Vancomycin levels ranged from 17-62 mcg/mL, so no specific threshold level was found. The ototoxicity is manifested by vestibular damage and/or cochlear damage, which leads to sensory hearing loss and tinnitus.<sup>6</sup>

The other reported toxicity associated with vancomycin use is nephrotoxicity. This effect, however, seems to be relatively rare when vancomycin is used as monotherapy. The generally accepted incidence of nephrotoxicity secondary to vancomycin monotherapy is <5% but increases to 43% in patients receiving concomitant nephrotoxic drugs (e.g., aminoglycosides, amphotericin B).<sup>6</sup> When reviewing cases, it is difficult to establish with certainty whether vancomycin is the cause of impaired renal function or whether vancomycin accumulation has occurred as a consequence of decreased renal function for other reasons.<sup>7</sup> Many of the early reported cases of nephrotoxicity occurred with impure preparations of vancomycin. Since the introduction of vancomycin and through the mid-1980's, early lots of vancomycin contained large amounts of fermentation broth impurities. The preparation was brown and was dubbed "Mississippi mud" because of its appearance.<sup>8</sup> Modern formulations have excellent safety profiles; however, reports of vancomycin-related nephrotoxicity still surface. Studies have been performed trying to establish a link between vancomycin serum concentrations and the risk for nephrotoxicity. Two studies found a greater risk of nephrotoxicity at trough levels greater than 10 mcg/mL when vancomycin was used with a nephrotoxic agent.<sup>9,10</sup> No correlation, however, was found between nephrotoxicity and peak vancomycin levels.

### **Concentration-efficacy Relationship**

A close relationship between drug dosage and resultant serum concentration and their relationship to minimum inhibitory concentration (MIC) and therapeutic outcome is ideal. Studies have been performed to try and correlate serum vancomycin levels with clinical outcomes. Zimmerman et al. studied 273 patients receiving vancomycin and found that patients whose trough concentrations were greater than 10 mcg/mL were more likely to become afebrile and have normal white blood cell count within 72 hours.<sup>11</sup> They did not, however, show positive effects on length of stay or overall mortality. Investigators in a prospective multicenter study (n=141) found no relationship between vancomycin peak and trough concentrations that predicted efficacy or toxicity, when the concentrations were prospectively adjusted and monitored to be maintained within target values of 30-40 and 5-10 mcg/ml, respectively.<sup>12</sup>

Vancomycin appears to follow concentration-dependent killing up to 1.0 mcg/mL. Above this level, it exhibits concentration-independent killing. This means the time above the MIC is important, not the peak concentration obtained (as is with aminoglycosides). Optimal bactericidal effects are found at concentrations 3-5 times the organisms MIC. Because the average vancomycin MIC for *Staphylococcus aureus* and *Staphylococcus epidermidis* are 1-2 mcg/mL, minimum predose or trough steady-state concentrations of 5-10 mcg/mL are usually adequate to resolve infections with susceptible organisms.

### **Sampling considerations**

Justification for monitoring peak concentrations with vancomycin is lacking for most populations. When peak concentrations are obtained, a few points must be kept in mind; (1) Vancomycin pharmacokinetics have been described by 1, 2 and 3 compartmental models, (2) The vancomycin concentration at 1 hr may be more than double that taken at 2 hr and still be within the recommended target range (3) To get accurate levels, one must be certain that the distribution phase is complete before the peak serum level is drawn. Peak serum levels have been drawn from 15 minutes to 2 hours post end of infusion. In order to interpret peak levels appropriately, the exact infusion time and exact draw time for the lab must be documented and reported.

Abandoning the measurement of peak vancomycin concentrations would eliminate the confusion surrounding their interpretation. Sanders has suggested that, provided the trough concentration is within recommended limits (<10-15 mcg/mL), the peak level (taken at 1-hr) is unlikely to fall into a potentially toxic range.<sup>13</sup>

**Indications for Monitoring Serum Vancomycin**<sup>7,14,15</sup>

- Monitoring is NOT recommended in the following settings:
  - Patients treated for less than five days.
  - Patients receiving oral vancomycin.
  - Patients with stable renal function who are treated for up to 14 days for mild to moderate infections.
  
- Vancomycin serum levels ARE recommended in the following settings:
  - Serious or life-threatening infections. TROUGH ONLY.
  - Patients receiving vancomycin/aminoglycoside or vancomycin/amphotericin B combination therapy. TROUGH ONLY.
  - Anephric patients undergoing hemodialysis and receiving infrequent doses of vancomycin for serious systemic infections. RANDOM TROUGH 4 hours after dialysis.
  - Patients receiving higher than usual doses of vancomycin (adults: > 20 mg/kg/dose, pediatrics: > 60 mg/kg/day). INITIAL PEAK & TROUGH. Once therapeutic, do not repeat levels if fluid status and renal function are stable.
  - Patients with rapidly changing renal function\*. RANDOM TROUGH only.
  - Morbidly obese patients. TROUGH ONLY.
  - Reaffirm a seriously abnormal or unusual serum concentration (i.e., line draws, inappropriate times, etc.).
  - Neonates: a) determine a therapeutic level has been achieved after culture results have been reported and b) monitor serum levels with prolonged therapy >10 days. INITIAL: PEAK AND TROUGH; TROUGH ONLY after therapeutic levels achieved for prolonged administration with stable renal function.
  - Patients receiving prolonged (>14 days) vancomycin therapy. TROUGH ONLY.

\*Rapidly changing renal function = 50% increase/decrease or 0.5 mg/dl increase/decrease in SCr over 24-48 hours.

<b>Serum Drug Levels</b>				
<b>Drug</b>		<b>Time to Obtain</b>	<b>Therapeutic Range</b>	<b>Hospital Cost</b>
Vancomycin * levels not routinely recommended *	Trough	½ hour before infusion	5-15 mcg/mL	\$9.71
	Peak	1 hour after infusion	25-40 mcg/mL	\$9.71

## Vancomycin Pharmacokinetic Calculations

### Definitions

IBW	=	ideal body weight
ABW	=	actual body weight
DBW	=	dosing body weight
kel	=	elimination rate constant
Vd	=	volume of distribution
$\tau$	=	dosing interval
t	=	time of infusion
t <sub>before</sub>	=	time between blood draw and start of infusion
t <sub>end</sub>	=	time from end of infusion to blood draw
t <sub>1/2</sub>	=	half-life
C <sub>max</sub>	=	peak serum level at steady-state
C <sub>min</sub>	=	trough serum level at steady-state
SCr	=	Serum creatinine

### Empiric Dosing – No Levels<sup>18</sup>

$$1. CrCl = \frac{(140 - \text{age}) \times IBW (\times 0.85 \text{ if female})}{72 \times SCr}$$

<b>Ideal Body Weight (IBW)</b>
Males: 50 kg + 2.3 kg per inch > 60 inches
Females: 45.5 kg + 2.3 kg per inch > 60 inches

2. Use population kinetics to calculate a dosing regimen (see Pharmacokinetic Pocket Card and use “empiric” formulas). Use ABW.

### Individualized Dosing (levels obtained) – Calculate patient-specific kel and Vd

$$1. kel = \frac{\ln (C_{max}/C_{min})}{\tau - (t + t_{end} + t_{before})}$$

$$2. C_{max_{actual}} = \frac{C_{max}}{e^{-kel(t_{end})}}$$

3. See Pharmacokinetic Pocket Card for specific Vd formulas under “After levels.”

4. If you want to adjust the dose, plug patient-specific kel and Vd into dose equations and verify appropriate levels with the equations for estimated peak and trough at steady state.

## References for Vancomycin

1. American Hospital Formulary Service (AHFS) Drug Information. ASHP, Bethesda MD.2003:470-477.
2. Drug Facts and Comparisons, 56<sup>th</sup> edition. Facts and Comparisons, St. Louis.2002:1393-1395
3. Micromedex<sup>®</sup> Healthcare Series. Thompson, Vol. 123: Exp. 3/2005.
4. Geraci JE, Heilman FR, Nichols DR, et al. Antibiotic therapy of bacterial endocarditis. VII. Vancomycin for acute micrococcal endocarditis: preliminary report. *Mayo Clin Proc* 1958;33:172-81
5. Cantu TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. *Clin Infect Dis* 1994;18:533-43
6. James CW, Gurk-Turner C. Recommendations for monitoring serum vancomycin concentrations. *BUMC Proceedings* 2001;14:189-90
7. Catchpole C, Hastings JGM. Measuring pre- and post-dose vancomycin levels – time for a change? *J Med Microbiol* 1995;45:309-11
8. Darko W, Medicis JJ, Smith A, et al. Mississippi mud no more: cost-effectiveness of pharmacokinetic dosage adjustment of vancomycin to prevent nephrotoxicity. *Pharmacotherapy* 2003;23(5):643-50
9. Cimino MA, Rotstein CM, Moser JE. Assessment of cost-effective antibiotic therapy in the management of infections in cancer patients. *Ann Pharmacother* 1994;28(1):105-11
10. Rybak MJ, Albrecht DM, Boike SC, et al. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. *J Antimicrob Chemother* 1990;25:679-87
11. Zimmermann AE, Katona BG, Plaisance KI. Association of vancomycin serum concentrations with outcomes in patients with gram-positive bacteremia. *Pharmacotherapy* 1995;15:85-91
12. Karam CM, McKinnon PS, Neuhauser MM, et al. Outcome assessment of minimizing vancomycin monitoring and dosing adjustments. *Pharmacotherapy* 1999;19(3):257-66
13. Saunders NJ. Why monitor peak vancomycin concentrations? *Lancet* 1994;344:1748-50
14. Drew RH. Vancomycin dosing and serum concentration monitoring in adults. UpToDate<sup>®</sup> Online 11.1, last changed 7/3/2001, accessed 6/17/02
15. Pryka RD. Vancomycin serum concentration monitoring: A continued debate. *Ann Pharmacother* 1994;28:1397-9.

# Clinical Pearls for Aminoglycosides and Vancomycin

## Aminoglycosides

- We assume that approximately 50% of the drug is removed by a standard hemodialysis session. For example, if the serum concentration prior to dialysis is 2.4 mcg/mL, we assume that it would be around 1.2 mcg/mL after dialysis.
- When indicated, we recommend obtaining a random level at least 2 hours after the end of a hemodialysis session to allow for redistribution. If levels are obtained sooner than this, especially immediately post-dialysis, the resultant level will be lower than the actual level because dialysis removes the drugs from the blood faster than they can redistribute from the tissues back into the bloodstream.

## Vancomycin

- We assume that approximately 20-30% of the drug is removed by a standard hemodialysis session. For example, if the serum concentration prior to dialysis is 18 mcg/mL, we assume that would be around 13.5 mcg/mL after dialysis.
- When indicated, we recommend obtaining a random level at least 4 hours after the end of a hemodialysis session to allow for redistribution. If levels are obtained sooner than this, especially immediately post-dialysis, the resultant level will be lower than the actual level because dialysis removes vancomycin from the blood faster than it can redistribute from the tissues back into the bloodstream.
- In general, we are more concerned with vancomycin troughs because it is a concentration-independent drug.
- For infections in which penetration is an issue (e.g., endocarditis, osteomyelitis, meningitis, pneumonia), the targeted trough level should be ~15 mcg/mL. There is a paucity of data to support or refute obtaining trough levels higher than this. Furthermore, when performing calculations, we usually aim for a peak close to 40 mcg/mL, based on the hypothesis that a high peak concentration will help drive drug into the tissues. Again, the data to support a peak higher than this are scarce to nonexistent.

## Dosing Gentamicin and Tobramycin in Patients with Cystic Fibrosis

Compiled by Erin Iselin, Pharm.D.

Patients with cystic fibrosis (CF) require higher than normal doses of these and many other antibiotics. Some investigators have suggested increased renal clearance while others suggest extra-renal enhancement of elimination. Some maintain Vd's are increased; others suggest that the Vd's normalized to BSA are similar to normal controls. It is apparent that the Vd does increase in patients with CF. This may be due to hypervolemia, especially in patients with cor pulmonale caused by extensive lung involvement. Half-lives are normally shorter.

Empirically dosing CF patients can be a tricky situation. We currently start patients receiving these antibiotics for the **first** time (no record of a previous dose from a previous hospitalization) on 10mg/kg/day divided Q 8 hours. Some authors suggest 80mg/M<sup>2</sup> given every 6 hours. The Director of Pediatric Pulmonology at The Nebraska Medical Center prefers not to use Q 6 hour intervals for patients with CF. Levels are normally obtained around the 3<sup>rd</sup> or 4<sup>th</sup> dose, whichever is more convenient for the patient and the pharmacist (waking hours). Typically, a peak returns around 6-8 mcg/ml. CF patients require the post-dose peak to be 10-11 mcg/ml (up to 12 gets risky). Trough levels should always remain  $\leq$  1mcg/ml. CF patients receive many doses of these antibiotics over the course of their lifetime, and we want to limit the side effects that can occur.

When CF patients are readmitted and placed on these antibiotics again, the previously required mg/kg/day dose is suggested. This is the dose that the patient was previously discharged on. No empiric calculations are needed in this situation. Assess the dose to determine the mg/kg/day is adequate and in the desired range. After the first levels, a slight adjustment may be required due to a change in the Vd.

Although it is not clearly understood, these antibiotics exhibit “pseudo-zero-order” kinetics at higher dosages (small dosage increases or decreases cause larger than anticipated changes in levels). If this is not recognized, a “yo-yo” effect occurs when trying to stabilize the levels (low-high-low). To avoid this, it is suggested not increasing the dose to more than 14mg/kg/day on the first upward dosage adjustment. Doses higher than 15mg/kg/day should be approached in a gradual stepwise fashion. When adjusting the dose for high peaks, calculate a new dose, take half to 60% of the difference (current dose – calculated dose) and subtract it from the current dose.

Example: Levels from 195mg q12h yielded 0.7/12.6 mcg/ml respectively

The new calculated dose= 160mg q12h

New recommended dose= 195mg – 160mg = 35 mg/2 = 17.5 mg; 195 mg – 17.5 mg = 177.5 mg → 180mg q12h estimated <1/10mcg/ml levels

These drugs exhibit pseudo-zero-order kinetics and adjusting the dose upward for a lower than desired peak needs careful consideration to avoid the yo-yo effect. Small adjustments of 10-20mg are all that is needed to increase the peak to the desired therapeutic level.

Following the achievement of therapeutic levels, it is suggested that levels be obtained at least weekly to assure they are not supratherapeutic. Sometimes a dosage adjustment of about 10% is required.

Dosage requirements for many other antibiotics are also higher for these patients. It appears that hepatic clearance of many drugs is increased, including some drugs which are normally excreted unchanged renally.

### **CLINICAL PHARMACOKINETIC CONSULT SERVICE**

- Automatically consult on all aminoglycoside and vancomycin orders.
- Consult on any other therapeutically monitored drug on request.
- Initial note (write “1<sup>st</sup> Dose Kinetics” in the spot for Dosing Regimen) – All new orders need to have an initial note written, predicting levels based on empiric (population) PK parameters, including our recommendations. The ONLY exceptions to 1<sup>st</sup> note are NICU, CF, and post-op (x ≤ 3 doses). \*\*However, ALL new orders still need to be checked for appropriateness\*\* (e.g., the NICU is based on a nomogram, CF patients’ doses are based on past doses and/or a mg/kg basis, post-op’s (esp AG’s) need to be changed if interval is not appropriate for patient’s age/renal function).
- Whenever levels are obtained, a note should be written (even if the levels weren’t ordered or the patient is not at steady-state). It is our job to interpret the levels. NOTE: When making a recommendation on whether or not to obtain levels, please refer to the guidelines on the bottom of the kinetics consult sheets (vancomycin and aminoglycosides). Levels should be obtained at steady state, which usually occurs at 5 times the half-life. Thus, this can help you figure out with which dose to obtain levels (usually the third dose for aminoglycosides and the third or fourth dose with vancomycin).
- Interventions (These require contact with the physician to inform them of your recommendations and document the interaction in RxFusion.)
  - Inappropriate initial dose regimen
  - Questionable levels – need to redraw
  - Potentially toxic or subtherapeutic levels
- We need to have a physician’s order to change or order anything.

- If we are specifically consulted by a physician (i.e., they write, “gentamicin, pharmacy to dose”), sometimes it is not necessary to call when changing the dose and ordering levels – depending on physician and patient (i.e., write order as a verbal order from Dr. \_\_\_\_\_).
- Every patient should be monitored EVERY DAY, and the monitoring calendar should be updated every day. (WBC, BUN, SCr, Tmax, cultures, etc.) NOTE: It is very important to document the microbiology reports on the back of the calendar.
- Communicate with the next pharmacist when levels are due, length of therapy, etc. This includes the central pharmacists, when necessary, on weekends and holidays (i.e., bring a consult form that has been started down to the central pharmacy).
- Old consults are in the kinetics file cabinet, with the CF patients’ files separated out. These should be consulted whenever possible!

## **NOTE WRITING**

Examples (There are many ways to write these notes.)

- Initial note:  
Gentamicin started for Pseudomonas UTI. Based on population pharmacokinetics and the patient’s estimated CrCl, would predict steady-state peak and trough on 120 mg IV q12h to be ~3-4 mcg/mL and < 2 mcg/mL, respectively. If desire more aggressive therapy, may consider 140 mg IV q12h for predicted peak and trough of ~5-6 mcg/mL and < 2 mcg/mL, respectively. Suggest checking levels around 3<sup>rd</sup> dose (when the drug will be at steady-state). Thank you for the consult. Pharmacy will continue to follow.
- Follow-up note:  
Gentamicin day #3. Peak level drawn 2 hours after end of infusion, therefore actual peak ~6 mcg/mL. Trough of 0.8 mcg/mL is optimal to minimize risk of oto/nephrotoxicity. Recommend continuing current dose and checking another trough in ~3 days. Thank you. Pharmacy will continue to follow.

## **OBJECTIVE OF NOTES**

- Initial assessment using population parameters or previous dosing
- Interpret levels (e.g., peak level of 10.2 mcg/mL appears to have been drawn early, therefore pre-distributional and falsely high)
- Recommend new regimen and when to start it, or continuing present dose
- Monitoring/follow-up (next levels, if any, SCr if necessary)
- Education – teaching hospital

## **TIPS**

- Give yourself some room when predicting levels (e.g., vancomycin trough 5-10 mcg/mL). Never put an exact number on the consult form when estimating levels. For example, if you calculate an expected vancomycin trough of 11.8 mcg/mL, put a range of +/- 1 (11-13 mcg/mL) on the form. This is not an exact science and should not be purported as such!
- If you calculated the estimated creatinine clearance via Cockcroft-Gault and it is > 100 ml/min, we round down to 100 ml/min (i.e., we do not use a value greater than 100 ml/min in our calculations) because this is typically the maximum value for adult men and women. Put “>100 ml/min” in the blank for CrCl, and use 100 ml/min in your calculations.
- Avoid blaming (e.g., “The level was drawn 1.5 h post-dose, estimate actual peak to be...” rather than, “The nurse drew the peak 1 hour late.”)
- Suggest/recommend (e.g., “if plan to continue, recommend checking a trough in ~3-5 days).
- Identify indication (e.g., *S. aureus* bacteremia, empiric treatment s/p abdominal abscess drainage rather than *S. aureus* or empiric treatment)
- Don’t diagnose (e.g., “possible pneumonia”)
- Limit liability
- Be professional
- \*ALWAYS READ CHART BEFORE WRITING NOTE\*