Aminoglycoside Pharmacokinetics

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Associate Professor of Pharmacy
Clickers

- The Tuesday recitation received clickers yesterday
- If you would like a clicker for this am, come to the front on the class with a pen to sign a contract
Clickers

- Turn clicker on by pressing down menu button
- Enter your OSU student ID number
- The up/down diagonal arrows button on the left is the button to SEND your answers
- The menu button is also used to turn your clicker off
  - But don’t turn it off now
- Raise your hand if you’re having trouble
- OK, let’s begin…
Goals

- Review the PK properties of aminoglycosides
- Compare and contrast methods of dosage regimen design for aminoglycosides
- Apply the PK model to develop and adjust individualized dosing regimens for patients
Objectives

Through the preparation for and participation in this lecture, a successful student should be able to:

- Identify the appropriate PK model and equations commonly used to dose aminoglycosides
- Describe the PK highlights of aminoglycosides, and identify the normal population PK parameters
- Discuss when peak and trough serum aminoglycoside concentrations should be obtained
- Determine appropriate target aminoglycoside concentrations for a given patient
Objectives

- Discuss adverse effects of aminoglycosides and relate to serum concentrations
- Identify those disease states known to influence the PK of aminoglycosides
- Compare and contrast synergistic, traditional, and extended-interval dosing methods of aminoglycosides. Know when it is appropriate to use each method, and how to monitor therapy.
- Given a patient history and therapeutic goal, develop a loading dose and maintenance dose regimen for aminoglycosides using dosing nomograms and an appropriate PK model.
Objectives

- Given a patient history, therapeutic goal and serum concentration data, calculate $k$ and $V_D$ and use to adjust the patient’s maintenance dose regimen
- Identify indications for monitoring serum aminoglycoside concentrations
- Develop a PK monitoring plan for a given patient receiving aminoglycosides
Aminoglycosides (IV/IM)

- Gentamicin
  - More active against *Serratia*
- Tobramycin
  - Most active against *Pseudomonas aeruginosa*
- Netilmicin
  - May be least ototoxic
- Amikacin
  - Least likely to develop resistance
- Kanamycin
  - Rarely used

Get your clicker ready
Select the TRUE statements:

A) Aminoglycosides are bactericidal
B) Aminoglycosides exhibit concentration-dependent killing
C) Aminoglycosides bind to the 30S ribosomal subunit, inhibiting protein synthesis and misreading of mRNA causing dysfunctional protein production
D) Aminoglycosides exhibit time-dependent killing and disrupt cell wall synthesis
E) A, B, and C are True
F) All of the above are True

Get your clicker ready
The graph depicts:

A) Concentration-dependent killing
B) The post antibiotic effect (PAE)
C) Adaptive resistance
D) No clue
Pharmacology

- Mechanism of action
  - Bactericidal, interferes with bacterial protein synthesis at 30S ribosome

- Post-antibiotic effect
  - No growth even when blood concentrations are minimal or absent
    - 0.6-7.5 hours

Get your clicker ready
Spectrum of Activity

- Primary target organisms include aerobic gram-negative bacteria
- Synergism at low doses for gram-positive organisms (staphylococci, enterococci)
- Used in combination for additive and synergistic effect against selected organisms
- Be familiar with institutional antibiogram
Clinical Uses

- Septicemia
- Urinary tract infections
- Pneumonia
- Endocarditis
- Prophylaxis in abdominal surgery
- Neutropenic patient with suspected infection
- Other infections caused by susceptible organisms
PK Highlights

- Prototype for drug totally eliminated by glomerular filtration
- Serum concentrations correlate with efficacy and toxicity
- Wide interpatient variability in disposition
- Evolving modes of administration
PK

- Low MW
- Weakly basic
- Water soluble
- Polar
- All are structurally similar
- All have similar PK properties
Absorption

- Oral F (poor, 0.3-1.5%)
- IM/IV F 100%
- IM
  - $T_{\text{peak}}$ approx 1 hour (0.5-2.0 hrs)
  - Avoid in critically ill patients
- $S = 1$
Distribution

- Distributed to extracellular water
  - 0.20 – 0.26 L/kg
- Significant accumulation in kidney cortex, and inner ear
- Distributes well to:
  - Ascitic, pericardial, peritoneal, pleural, synovial fluids
- Crosses placenta
  - Fetal concentrations are 16-50% of maternal concentrations
- Poor distribution into CSF and vitreous humor
<table>
<thead>
<tr>
<th>Volume of Distribution</th>
<th>Range</th>
<th>Average (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>0.07 – 0.7</td>
<td>0.26 L/kg</td>
</tr>
<tr>
<td>Child</td>
<td>0.07 – 0.7</td>
<td>0.45 L/kg</td>
</tr>
<tr>
<td>Neonate</td>
<td>0.2 – 0.6</td>
<td></td>
</tr>
</tbody>
</table>
Gentamicin Distribution Volume

1369 Patients
Normal Renal Function
Mean (± S.D.) = 0.19 ± 0.08 L/kg
Factors Affecting Distribution

- Increased $V_D$
  - Obesity
  - Ascites
  - Cystic fibrosis
  - Pregnancy/post-partum
  - Edema

- Decreased $V_D$
  - Dehydration
Protein Binding

- 0-30%
Elimination

- Route
  - Almost totally excreted unchanged in urine via glomerular filtration

- Complete recovery of a single dose in urine takes 10-20 days with normal renal function due to slow release from deep tissue compartment
Factors Affecting Disposition of Aminoglycosides
Renal Function

\[ y = mx + b \]
\[ k = 0.00293 \text{ [CrCl ml/min/1.73m}^2\text{]} + 0.019 \]
\[ n=1640 \text{ pts ; } r^2 = 0.34 \]
Get your clicker ready
Based on the previous graph,

A) As renal function declines, the elimination rate constant decreases, and half life increases.

B) As renal function increases, the elimination rate constant increases, and half life decreases.

C) One can predict aminoglycoside k by knowing creatinine clearance.

D) All of the above are true.
<table>
<thead>
<tr>
<th>Age Group</th>
<th><code>T_{1/2}</code> (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult SCr ≤ 1.5 mg/dl</td>
<td>0.4 – 32.7 (mean 1.5-2.0 hrs)</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>0.5 – 2.5</td>
</tr>
<tr>
<td>Neonates 1st month of life</td>
<td>2.0 – 9.0</td>
</tr>
</tbody>
</table>
Gentamicin Half-life

1369 Patients
Normal Renal Function
Mean (± S.D.) = 2.2 ± 2.1 hrs
Pediatrics

- **Neonates**
  - Dynamic changes in cardiac output, renal blood flow, renal function, and extracellular fluid (ECF)
  - $V_D = 0.6 - 0.9 \text{ L/kg}$
  - $T_{1/2} = 0.9 - 2 \text{ hrs}$
  - $CL = 1.1 - 1.3 \text{ ml/min/kg}$
Pediatrics

- Children
  - $V_D = 0.4 \text{ – } 0.49 \text{ L/kg}$
  - $T_{1/2} = 0.9 \text{ – } 2.0 \text{ hr}$
  - $CL = 123 \text{ – } 195 \text{ ml/min}$
Issues

- Usually begin with mg/kg standard doses q 6 – 12 hours
- Renal function changes
140 kg Obese Patient with Ideal Body Weight of 70 kg

Lean tissue (70 kg)

Adipose tissue (70 kg)

ECF content
Obesity

- Aminoglycosides distribute into ECF in fat tissues; however, fat tissue has less ECF than lean tissue
- Morbidly obese have increased CrCl
- Correction factor for $V_D$ in obese patients ($TBW > 1.5 \times IBW$):
  - $V_D = 0.26 \text{ L/kg} \left[ IBW + 0.4 \left( TBW - IBW \right) \right]$
- Morbidly obese patients:
  - $V_D = 0.18 \text{ L/kg} \ TBW$
Burn Patients

- Hypermetabolic
- Increased $V_D$
  - Increased ECF
    - Large volume fluids
  - Increased CL
    - Increased GFR
Cystic Fibrosis

- Increased $V_D$
  - Poor correlation with weight
- Increased CL
  - Poor correlation of $k$ with CrCl
  - Variable $t_{1/2}$ during therapy
- Get your clicker ready
What do these pictures show?

A) Ascites
B) Pregnancy
C) Tumor
D) Obesity
$V_D$ in ascites would be expected to:

A) Increase
B) Decrease
C) I can’t tell from the images
Ascites

- Fluid shifts
  - Before and after paracentesis
  - \( V_D = (0.26 \text{ L/kg} \times Wt_{NO \text{ ascites}}) + (1 \text{ L/kg} \times \text{Ascites Volume}) \)
Get your clicker ready
What does this picture show?

A) Ascites
B) Pregnancy
C) Tumor
D) Obesity
$V_D$ in pregnancy would be expected to:

A) Increase
B) Decrease
C) I can’t tell from the images
Obstetric Patients

- $V_D$
- Increased CL
  - Varies
  - Returns to baseline post-partum
Pregnancy category D

- All trimesters
- Crosses placenta
- Risks of fetal ototoxicity (8th cranial nerve toxicity)
- Congenital deafness has been reported with streptomycin, kanamycin during pregnancy
- Use if benefits outweigh risks; no alternative antibiotics
Breast milk

- Do the AG appear in breast milk?
  - Tobramycin 80 mg IM -> 0.6 mcg/ml and 0.85 mcg/ml at 1 and 8 hrs post-dose (low)
    - Brogden, et al 1976
  - “Although AG appear in breast milk, unlikely that any adverse effect would be experienced by the nursing infant.”
    - Micromedex
Toxicity

- **Ototoxicity**
  - 3 – 10% incidence

- **Vestibular damage**
  - Not reversible
  - Most patients compensate

- **Auditory damage**
  - Reversible in about 50% of patients
Get clicker ready.
What are risk factors for ototoxicity? Choose all that apply...

A) Prior or concurrent use of ototoxic drugs
B) Increasing age of patient
C) Compromised renal function and/or dialysis
D) Duration of therapy
E) Total dose of aminoglycosides
F) Dehydration
Weak Relationship with Serum Concentrations

- $C_{\text{max}} > 12 - 14 \text{ mcg/ml}$
  - $C_{\text{max}} > 32 - 34 \text{ mcg/ml}$ for amikacin
- $C_{\text{min}} > 2 \text{ mcg/ml}$
  - $C_{\text{min}} > 8 - 10 \text{ mcg/ml}$ for amikacin
- AUC
Monitoring

- Audiometry
- Electronystagmography
- Vomit comet
- Serum concentrations
- S/Sx
  - ataxia, nystagmus, vertigo, dizziness (vestibular), tinnitus, hearing loss
Nephrotoxicity

- <1 – 25% incidence
- Definition
  - Increase in SCr by 0.5 mg/dl if SCr < 2.0 mg/dl
  - Increase in SCr by 30% if SCr > 2 mg/dl
Characteristics

- Usually reversible renal impairment caused by damage to proximal tubule
  - AG bind to brush border, accumulation in proximal tubular epithelial cell in lysosomal phospholipid complexes; uptake is saturable
  - Eventual rupture resulting in cell death, activating renin-angiotensin system, local vasoconstriction and dec. GFR (inc. SCr), ATN, non-oliguric renal failure
  - Hypothesis: EID provides period where AG could leach back into lumen and dec. rate of accumulation

Nephrotoxicity

- Rise in SCr late marker
  - Obtain 1 – 2 x/week
- Rise in BUN
- Urinalysis (U/A)
  - Casts, proteinuria
Clinical Presentation

- Gradual, progressive, nonoliguric renal failure
  - Urine output < 20 ml/hr
  - Onset 2 – 7 days
- Followed by proteinuria, a progressive fall in GFR, and a rise in SCr
- Generally self-limiting and reversible in 10 – 30 days
Weak Relationship with Serum Concentrations

- $C_{\text{min}} > 2 \text{ mcg/ml}$ for tobramycin, gentamicin
- $C_{\text{min}} > 8 - 10 \text{ mcg/ml}$ for amikacin
Get your clicker ready
What are risk factors for nephrotoxicity? Choose all that apply...

A) Prior or concurrent use of nephrotoxic drugs
B) Increasing age of patient
C) Compromised renal function and/or dialysis
D) Duration of therapy
E) Total dose of aminoglycosides
F) Dehydration, hypovolemic
Desired Aminoglycoside Serum Concentrations

- Depends on:
  - Bacteria causing infection
  - Site of infection
  - Type of infection
  - Clinical situation of patient
  - Intent of therapy
Dosing Strategy

- Synergy
- Traditional Dosing
- Extended-Interval Dosing
Aminoglycoside Infusion Guidelines

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Infusion Duration (min)</th>
<th>Time to draw peak (min after start of infusion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synergy</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Traditional</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>AG- EID</td>
<td>60</td>
<td>90</td>
</tr>
</tbody>
</table>

- All trough values should be drawn immediately prior to next dose (within 30 min of next dose)
- All serum levels should be drawn from an IV site other than the IV site utilized for infusion of the drug
- For EID, often prefer to draw random level 12-18 hours after initiation of infusion, rather than standard peak/trough
Synergy

- Gram-positive organisms
  - Egs. Staphylococci, streptococci, enterococci
  - Used in combination with B-lactam antibiotics or vancomycin
  - Targets low peak/trough values
  - Usual dose 1 – 1.5 mg/kg; interval based upon CrCl
Traditional Dosing

- For gram-negative pathogens
- Loading dose
- Target serum concentrations dependent upon severity/site of infection
- More frequent dosing in setting of good renal function (q8h, q12h) vs extended interval
- Utilized for exclusions of extended-interval dosing (EID)
Monitoring

- Traditional Dosing
  - Recommend peak/trough within 72 hrs of initiation and at least trough q 3-5 days thereafter, unless altered PK dictates more frequently
  - For pt w/ initial peak/trough, stable PK parameters, and continued clinical improvement, may spot check trough only
Considerations for checking peak and trough or more frequent monitoring

- Critically ill pts
- Site of infection (endocarditis, osteomyelitis…)
- Poor therapeutic response
- Suspected unusual PK
- Concurrent oto- or nephrotoxic agents
- Unusually high MIC values
- Severe renal impairment
## Traditional Dosing
### General Guidelines

<table>
<thead>
<tr>
<th>Infection</th>
<th>Tobramycin Peak (mcg/ml=mg/L)</th>
<th>Gentamicin Peak (mcg/ml=mg/L)</th>
<th>Netilmicin Peak (mcg/ml=mg/L)</th>
<th>Trough (mcg/ml=mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less severe Soft tissue</td>
<td>5 - 8</td>
<td></td>
<td></td>
<td>0.5 - 1.0</td>
</tr>
<tr>
<td>Severe</td>
<td>Up to 8 - 10</td>
<td></td>
<td></td>
<td>1 - 2</td>
</tr>
<tr>
<td>Sepsis, pneumonia, Burn pt, Immunosuppressed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Traditional Dosing

## General Guidelines

<table>
<thead>
<tr>
<th>Infection</th>
<th>Amikacin Peak (mcg/ml=mg/L)</th>
<th>Trough (mcg/ml=mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less severe</td>
<td>20 – 25</td>
<td>1 – 4</td>
</tr>
<tr>
<td>Soft tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>25 – 30</td>
<td>4 – 8</td>
</tr>
<tr>
<td>Sepsis, pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burn pt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Traditional method
Path to follow for starting dose using population PK parameters (Sawchuk-Zaske)
Determine CrCl

- For this exercise, use Cockroft & Gault
- We will discuss the various methods for calculating glomerular filtration rate (GFR) or creatinine clearance (CrCl) in the renal PK topics
Cockroft & Gault

\[
\text{CrCl}(\text{ml/min}) = \frac{(140 - \text{age})}{(72 \cdot \text{Scr})} \times \text{IBW}(0.85 \text{ females})
\]

- **M**: IBW (kg) = 50 kg + 2.3 (Ht. Inches > 5’)
- **F**: IBW (kg) = 45.4 kg + 2.3 (Ht. Inches > 5’)

**Features:**
- For patients Scr < 4.5 mg/dl; within 30% of IBW; age ≥ 18 years
- Requires steady-state Scr values
  - Ref: Nephron 1976;16:31-41
Weight Considerations

- $Wt = IBW$ for non-obese patients
- $Wt = $ Actual body weight if patient weighs less than IBW
- Use Adjusted Body Weight for obese patients*

**Definitions**
- Obese: TBW greater than $1.2 \times IBW$
- Morbidly Obese: TBW equal or greater than $2 \times IBW$

- $Wt$ for CrCl in obese patients:
- Obese CrCl $Wt = IBW + 0.4(TBW - IBW)$
Renal Function

\[ y = mx + b \]

\[ k = 0.00293 \text{ [CrCl ml/min/1.73m}^2\text{]} + 0.019 \]

\( n = 1640 \text{ pts} ; r^2 = 0.34 \)
Elimination Rate Constant (k)

- Determine \( k \) (Dettli method)
  
  \[
  k \text{ (hr}^{-1}\text{)} = 0.00293 \left[ \text{CrCl ml/min/1.73m}^2 \right] + 0.019
  \]

  \[
  \text{BSA (m}^2\text{)} = \text{TBW (kg)}^{0.425} \times \text{Ht (cm)}^{0.725} \times 0.007184
  \]

  - 2.54 cm/inch
Use CrCl in ml/min/1.73m$^2$

- Often not done
- Pt’s CrCl (ml/min): Pt’s BSA (m$^2$)
- as $x$CrCl (ml/min/1.73 m$^2$): 1.73 m$^2$
- Solve for $x$:

$$ CrCl_{ml/ min/1.73m^2} = Pt'sCrCl(ml/ min) \times \frac{1.73m^2}{Pt'sBSA(m^2)} $$
Half-life ($t_{1/2}$)

- Determine $t_{1/2}$ (hrs) = 0.693/k
Volume of Distribution ($V_D$)

- $V_D (L) = 0.25 \text{ L/kg} \times \text{ ideal body weight}$

- Obese pts:
  - $V_D (L) = 0.25 \text{ L/kg} \ (\text{IBW} + 0.4 \ (\text{TBW} - \text{IBW}))$

- Pts w/ ascites
  - $V_D (L) = (0.25 \text{ L/kg})(\text{IBW}) + (\text{Excess 3rd Space Fluid Weight in Liters})$
Determine Need for Loading Dose (LD)

\[ LD = \frac{C_{\text{max,desired}} \ast V_D}{SF} \]
Optimum Dosing Interval (\(\tau\))

\[
\tau = -\frac{1}{k} \left[ \ln \frac{C_{\min, desired}}{C_{\max, desired}} \right] + t
\]

\(\tau\) = dosing interval

Small \(t\) = infusion time

Note this is a rearrangement of the equation \(C_{\min} = C_{\max} \times e^{-k(Tau-t)}\)
Short IV Infusions

\[ C_{\text{max}1} = \frac{\text{dose} / t}{V_D k} \left( 1 - e^{-kt} \right) \text{ OR } \frac{\text{dose} / t}{CL} \left( 1 - e^{-kt} \right) \]

\[ C_{\text{min}1} = C_{\text{max}1} e^{-k(Tau-t)} \]

\[ C_{\text{max,ss}} = \left( \frac{\text{dose} / t}{CL} \left( 1 - e^{-kt} \right) \right) \left( \frac{1}{1 - e^{-kTau}} \right) \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)} \]

- small \( t = t = \) infusion time
- \( tau = \) dosing interval
Short IV Infusions

- Recall,
- $\frac{\text{dose}}{t} = \text{rate of drug infusion}$
- $1 - e^{-kt} = \text{fraction of SS achieved by time } t \text{ OR fraction of drug lost during time } t$
- $e^{-k(Tau-t)} = \text{fraction of drug remaining at end of dosing interval}$
- $= \text{time } tau \text{ minus } t$
- $R_{ac} = \text{accumulation factor, allows you to fast forward to steady-state (SS)}$

rate in over rate out

$$C_{\text{max,1}} = \frac{\text{dose} / t}{V_D \cdot k} \left(1 - e^{-kt}\right)$$

$$C_{\text{min,1}} = C_{\text{max,1}} e^{-k(Tau-t)}$$

$$C_{\text{max,ss}} = \left(\frac{\text{dose} / t}{V_D \cdot k} \left(1 - e^{-kt}\right)\right) \left(\frac{1}{1 - e^{-kTau}}\right)$$

$$C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)}$$
Optimum Dose

\[ C_{\text{max}} = \left( \frac{dose/t}{V_D \ast k} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{1 - e^{-k\tau}} \right) \]

Solve for dose/t

\[ \frac{dose}{t} = V_D \ast k \ast C_{\text{max,desired}} \left( \frac{1 - e^{-k\tau}}{1 - e^{-kt}} \right) \]
Double check

Use optimal dosing regimen suggested to determine expected $C_{\text{min}}$ and $C_{\text{max}}$
Short IV Infusions

\[ C_{\text{max,ss}} = \left( \frac{\text{dose} / t}{V_D k} \right) \left( 1 - e^{-kt} \right) \left( \frac{1}{1 - e^{-k\tau}} \right) \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)} \]

- small \( t = t = \) infusion time
- \( \tau = \) dosing interval
Path to follow for working from known concentrations
Mechanics of Obtaining Serum Concentrations

- Trough Before Dose
- Peak After Distribution
- At SS, assume trough

\[ \text{Log } C_p \]

- Dose Infused IV
- Delta time! = \tau - t
Get your clicker ready
Example

- AM was prescribed tobramycin 100 mg over 30 min every 12 hours (0800, 2000). Tobramycin concentrations were obtained around the 4th dose, given at 0800. The concentrations are as follows:
  - Time 0800; tobramycin 0.5mcg/ml
  - Time 0900; tobramycin 8.0mcg/ml
Mechanics of Obtaining Serum Concentrations

Dose Infused IV

Trough Before Dose 0800

Peak After Distribution 0900

At SS, assume trough 2000 next dose

Log $C_p$

Delta time!

Time

Dose Infused IV

Dose Infused IV

Dose Infused IV
In order to calculate $k$, we assume that $\Delta t$ is:

A) The difference between 0800 and 0900, which is 1 hour

B) The difference between 0900 and 2000 before the next dose, which is 11 hours

C) I can’t tell from the graph
Elimination Rate Constant (k)

\[-k = \frac{\ln C_2 - \ln C_1}{\Delta t}\]

This equation will give you a negative value.

-\(k\) = negative number,
therefore + \(k\) = positive number

or

\[k = \frac{\ln \left( \frac{C_1}{C_2} \right)}{\Delta t}\]
Example

- AM was prescribed tobramycin 100 mg over 30 min every 12 hours (0800, 2000). Tobramycin concentrations were obtained around the 4\textsuperscript{th} dose, given at 0800. The concentrations are as follows:

  - Time 0800; tobramycin 0.5mcg/ml
  - Time 0900; tobramycin 8.0mcg/ml
Elimination Rate Constant (k)

This equation will give you a negative value.
-k = negative number,
therefore + k = positive number

\[-k = \frac{\ln C_2 - \ln C_1}{\Delta t} = \frac{\ln 0.5 - \ln 8}{11\text{hrs}} =\]

or

\[k = \frac{\ln \left( \frac{C_1}{C_2} \right)}{\Delta t} = \frac{\ln \left( \frac{8}{0.5} \right)}{11\text{hrs}} =\]

Record your answer, then calculate \( t_{1/2} \)
Get your clicker ready
Calculate $k$ & $t_{1/2}$

A) $k = 1.39 \text{ hr}^{-1}$; $t_{1/2} = 0.5 \text{ hrs}$

B) $k = 0.25 \text{ hr}^{-1}$; $t_{1/2}$ approx. 2.7 hrs

C) I can’t tell.
PK- Distribution

![Graph showing PK distribution with time in hours on the x-axis and serum concentration on the y-axis. The graph includes points labeled as alpha and beta, and markers for true PK, extrap PK, and measured PK.](image-url)
Determine patient $C_{\text{max}} \& C_{\text{min}}$

$$C_t = C_{\text{max}} e^{-kt}$$

or

$$C_{\text{max}} = \frac{C_t}{e^{-kt}}$$
If $C_{\text{max}}$ & $C_{\text{min}}$ acceptable, continue dosing.
If not, determine new regimen.
Volume of Distribution ($V_D$)

$$V_D = \frac{dose / t}{k} \cdot \frac{1 - e^{-kt}}{C_{\text{max}} - (C_{\text{min}} e^{-kt})}$$

Small $t$ = infusion time
Optimum Dosing Interval (\(tau\))

\[
\tau = -\frac{1}{k} \ln \left( \frac{C_{\text{min,desired}}}{C_{\text{max,desired}}} \right) + t
\]

Tau = dosing interval

Small \(t\) = infusion time
Optimum Dose

\[
C_{\text{max}} = \left( \frac{\text{dose} / t}{V_D \cdot k} \left(1 - e^{-kt}\right) \right) \left( \frac{1}{1 - e^{-k\text{tau}}} \right)
\]

\[
dose / t = V_D \cdot k \cdot C_{\text{max, desired}} \left( \frac{1 - e^{-k\text{tau}}}{1 - e^{-kt}} \right)
\]

- Solve for \( \text{dose} / t \)
Short IV Infusions

\[ C_{\text{max1}} = \frac{\text{dose}}{t} \left( 1 - e^{-kt} \right) OR \frac{\text{dose}}{t} \left( 1 - e^{-kt} \right) \]

\[ C_{\text{min1}} = C_{\text{max1}} e^{-k(Tau-t)} \]

\[ C_{\text{max,ss}} = \left( \frac{\text{dose}}{t} \left( 1 - e^{-kt} \right) \right) \left( \frac{1}{1 - e^{-kTau}} \right) \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)} \]

- small \( t = t = \text{infusion time} \)
- \( \text{tau} = \text{dosing interval} \)
Short IV Infusions

- Recall,
- \( \text{dose/t} = \text{rate of drug infusion} \)
- \( 1 - e^{-kt} \) = fraction of SS achieved by time \( t \) OR fraction of drug lost during time \( t \)
- \( e^{-k(Tau-t)} \) = fraction of drug remaining at end of dosing interval
- \( \text{R}_{ac} = \text{time tau minus t} \)
- \( \text{R}_{ac} = \text{accumulation factor, allows you to fast forward to steady-state (SS)} \)

\[
C_{\text{max,1}} = \frac{\text{dose/} \, t}{V_D \, k} (1 - e^{-kt})
\]

\[
C_{\text{min,1}} = C_{\text{max,1}} e^{-k(Tau-t)}
\]

\[
C_{\text{max,ss}} = \left( \frac{\text{dose/} \, t}{V_D \, k} (1 - e^{-kt}) \right) \left( \frac{1}{1 - e^{-kTau}} \right)
\]

\[
C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)}
\]
Short IV Infusions

\[ C_{\text{max,ss}} = \left( \frac{\text{dose}}{\text{t}} \right) \left( \frac{1 - e^{-kt}}{CL} \right) \left( \frac{1}{1 - e^{-k\tau}} \right) \]

\[ C_{\text{min,ss}} = C_{\text{max,ss}} e^{-k(Tau-t)} \]

- small \( t = \tau = \text{infusion time} \)
- \( \tau = \text{dosing interval} \)
Extended Interval
Aminoglycoside PK

Get your clicker ready
Which of the following statements are true regarding aminoglycoside pharmacodynamics?

A) Aminoglycosides exhibit concentration-dependent killing; however, the upper limit of $C_{\text{max}}$ is unknown

B) Aminoglycosides have a concentration-dependent post-antibiotic effect. The higher the $C_{\text{max}}$, the longer the PAE.

C) Aminoglycosides exhibit adaptive resistance

D) All of the above are true
Pharmacodynamics

- Concentration-dependent activity
  - Increased bactericidal activity with increased $C_{\text{max}}$
  - Target $C_{\text{max}}$ : MIC ratio $\geq 8 - 10 : 1$
    - Optimize bactericidal activity and PAE
- Post antibiotic effect (PAE)
  - Continuous suppression of bacterial growth despite decline of antibiotic concentration below MIC
  - Duration dependent upon organism and $C_{\text{max}}$

Get your clicker ready
Adaptive Resistance - Bacteria

- A period of resistance to bactericidal activity following initial aminoglycoside exposure
- Post-exposure down-regulation of aminoglycoside uptake
- Reduced bactericidal activity
- Reduced PAE
- Transient and reversible
- Duration of adaptive resistance is directly related to $t_{1/2}$
- Extending the dosing interval (tau) may increase efficacy by allowing time for reversal of adaptive resistance and the return of bacterial susceptibility

Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance of effective dosage regimens. Drugs 2001;61(6):713-21
In vitro

Barclay ML, Begg EJ. Aminoglycoside adaptive resistance: importance of effective dosage regimens. Drugs 2001;61(6):713-21
Anatomy
Nephron
Saturable Uptake - Kidneys

- Saturable uptake of aminoglycoside into renal cortical tubular cells

Tubular Lumen

Tubular Cell

AG

Toxicity

↑↑ AG

Saturable uptake of aminoglycoside into renal cortical tubular cells
Extended Interval Dosing

- EID may provide a period for aminoglycoside to leach back into lumen and reduce rate of aminoglycoside accumulation
Get your clicker ready
Please make your selection

A) In bacteria, exposure to AG causes down-regulation of uptake (adaptive resistance) which can be overcome by EID

B) On the other hand, uptake of AG into renal tubular cells is saturable, therefore if we increase the dose and increase $C_{\text{max}}$ with EID, then we can maximize efficacy and minimize toxicity

C) EID may provide a period for aminoglycosides to leach back into the renal tubular lumen (for renal excretion), thus minimizing toxicity

D) All of the above are true
Extended-Interval Dosing

- Pharmacodynamic goals
  - Peak $\geq 8 - 12 \times$ MIC
  - Trough $< 0.5$ mcg/ml
  - 3 – 5 hour drug-free interval at end of dosing interval
    - Minimize toxicity
    - Permit reversal of adaptive post-exposure resistance
EI D Exclusions

- Pregnancy/post-partum
- Renal failure (CrCl < 30 ml/min)
- Rapid clearance
  - +/- Cystic fibrosis
  - Extensive burn (>20% BSA)
- Severe hepatic disease (eg. ascites)
- Enterococcal endocarditis
- Hearing loss/vestibular dysfunction
- Highly variable or altered PK

ODD vs. MDD Effect on Enzyme Markers/Nephrotoxicity

- 58 critically-ill pts w/ documented or suspected gram-negative infection
- Randomized to tobra ODD (7 mg/kg once daily) or MDD (Sawchuk-Zaske nomogram)
- Baseline urine aliquots and 24h collection days 3, 7, 11 during therapy and days 3, 7, 11 after d/c of therapy for measurement AAP, NAG, SCr
- Tobramycin serum concentrations:
  - ODD: 1h and 10h after 1st dose and at min day 7
  - MDD: pk/tr after 4th or 5th dose
  - Doses adjusted as appropriate to maintain MDD- pk 6-10 mg/l, trough < 2 mg/l; ODD- using nomogram
- 54 pts evaluable
### Once Daily (ODD) vs. Multiple Daily Dosing (MDD) Effect on Enzyme Markers/Nephrotoxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>ODD (n=25)</th>
<th>MDD (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs (range)</strong></td>
<td>46.1 +/- 12.5 (21-69)</td>
<td>51.2 +/- 14.2 (20-74)</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Wt, kg</strong></td>
<td>70.1 +/- 14.1</td>
<td>80.8 +/- 35.5</td>
<td>0.056</td>
</tr>
<tr>
<td><strong>CrCl, ml/min baseline</strong></td>
<td>76.3 +/- 18.1</td>
<td>77.3 +/- 18.7</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>CrCl, ml/min end of therapy</strong></td>
<td>70 +/- 18.6</td>
<td>64.8 +/- 17.5</td>
<td>0.047</td>
</tr>
<tr>
<td><strong>Nephrotoxicity n (%)</strong></td>
<td>5 (20)</td>
<td>12 (41)</td>
<td>0.142</td>
</tr>
<tr>
<td><strong>Mean days therapy</strong></td>
<td>7.8 +/- 7.5</td>
<td>6.9 +/- 5.4</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Total daily dose, mg</strong></td>
<td>452 +/- 122.5</td>
<td>314.8 +/- 116.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean tobra serum conc.</strong></td>
<td>16.3 +/- 3.2</td>
<td>7.6 +/- 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>AUC, mg*hr/L</strong></td>
<td>110 +/- 38.7</td>
<td>93.8 +/- 33.9</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Enzyme Markers

- Recall, AG bind to brush border, accumulation in proximal tubular epithelial cell in lysosomal phospholipid complexes, cells rupture -> NTX
  - Called lysosomal phospholipidosis

- Early enzyme markers of early renal injury
  - Urinary enzymes are released by damaged proximal tubular cells
  - Urinary phospholipid excretion
    - Alanine aminopeptidase (AAP)
    - N-acetyl-β-D-glucosaminidase (NAG)
Early Nephrotoxicity

Effect of ODD vs. MDD of Tobramycin on Enzyme Markers of Nephrotoxicity  
(Crit Care Med 2004)

Evaluation of Nomograms

- PK analysis of four EID nomograms
  - Hartford Hospital
  - Barnes-Jewish Hospital
  - University of Rochester
  - Sanford Guide

<table>
<thead>
<tr>
<th>Nomogram</th>
<th>Gent dose (mg/kg)</th>
<th>Dose Interval (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CrCl &gt; 60 ml/min</td>
</tr>
<tr>
<td>Hartford Hospital</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Barnes-Jewish Hospital</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>University of Rochester</td>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

*30-39 ml/min only

# Sanford Guide

<table>
<thead>
<tr>
<th>Interval (hrs)</th>
<th>Dose (mg/kg)</th>
<th>Interval (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>5.1</td>
<td>24</td>
</tr>
<tr>
<td>60-79</td>
<td>4.0</td>
<td>24</td>
</tr>
<tr>
<td>40-59</td>
<td>3.5</td>
<td>24</td>
</tr>
<tr>
<td>30-39</td>
<td>2.5</td>
<td>24</td>
</tr>
<tr>
<td>20-29</td>
<td>4.0</td>
<td>48</td>
</tr>
</tbody>
</table>
Methods

- Collected serum aminoglycoside concentrations to determine PK parameters
- Compared nomogram-based dosing to individualized PK-based dosing to achieve target $C_{\text{max}}$ of 20 mcg/ml and target $C_{\text{max}} : \text{MIC}$ ratio $> 10$ or greater for bacteria with an MIC of 2 mcg/ml.
The recommended doses and resultant $C_{\text{max}}$ produced by the nomograms were significantly less ($p < 0.05$) than the dosage and $C_{\text{max}}$ needed to achieve target $C_{\text{max}} : \text{MIC}$ ratio > 10 or greater for bacteria with an MIC of 2 mcg/ml.
Evaluation of Nomograms

- Conclusion: EID using all four nomograms resulted in inaccurate dosing... due to large variability in pk, dosing nomograms should be abandoned in favor of individualizing dosages w/ therapeutic drug monitoring.

Conclusions EID

- Increased PK promotes improved bactericidal activity and longer PAE

- EID at least as efficacious as MDD

- EID no more nephrotoxic than MDD
  - Reduces renal cortical AG accumulation
  - May result in reduced toxicity
Monitoring

- High interpatient variability in PK parameters
- EID: little uniformity for recommendations
  - Predict PK (dose/Vd)
  - Population (or pt specific) $t_{1/2}$
  - Random level - when anticipate 1-2 mcg/ml
  - Timing based upon population/patient pharmacokinetic parameters and feasibility of draw time
  - Use random level to assess time above MIC and to minimize toxicity
## Target Serum Concentrations

<table>
<thead>
<tr>
<th>Dose Strategy</th>
<th>Target Peak (mcg/ml)</th>
<th>Target Trough (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synergy</td>
<td>3-5</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Traditional</td>
<td>5-10</td>
<td>≤ 2</td>
</tr>
<tr>
<td>Extended Interval</td>
<td>12-24</td>
<td>&lt; 0.5</td>
</tr>
</tbody>
</table>