Clinical Vancomycin and Aminoglycoside PK/PD

Andrew Berti, Pharm.D. Ph.D.
Pharmacy Practice Division
Research Fellow
andrew.berti@wisc.edu

Lecture Objectives and Readings

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Objectives
1. Understand the pharmacokinetic and pharmacodynamic (PK/PD) principles of vancomycin and aminoglycosides
2. Apply the principles of PK/PD to a given patient case as it relates to choice and dosage design
3. Understand PK/PD factors associated with efficacy, toxicity, and antibiotic resistance

Readings
   Summary of recommendations provided in Table 2.
2. Pharmacotherapy: A Pathophysiologic Approach 8th ed. Section 1.8: Clinical Pharmacokinetics and Pharmacodynamics

Pharmacokinetics: Concentration vs. Time Profile Single Dose

<table>
<thead>
<tr>
<th>Conc</th>
<th>Time</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cp max = Peak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cp min = Trough</td>
<td></td>
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</tbody>
</table>

Pharmacodynamic Parameters & Outcome

<table>
<thead>
<tr>
<th>Conc</th>
<th>Time</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax / MIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC / MIC</td>
<td></td>
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</tr>
</tbody>
</table>

Aminoglycosides

- Aminoglycosides
  - Gentamicin, tobramycin, amikacin
- Standard Dosing - normal renal function
  - Gentamicin/tobramycin - 2 mg/kg every 8-12 h
  - Amikacin 7.5 mg/kg every 12 h
- Used in serious Gram-negative and gram-positive infections
- Concentration dependent antibiotics
- Narrow therapeutic window
- Associated with renal (5-15%) and ototoxicity
  - Increased risk with high troughs and long duration
Application of Pharmacodynamic Principles: Aminoglycosides

- Rationale for single-dose aminoglycosides
  - Higher peak concentrations should increase efficacy
  - Significant PAE allows for longer dosing intervals
  - Lower trough concentrations should improve safety
  - Longer dosing intervals may decrease resistance

Aminoglycoside Key Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gentamicin and Tobramycin</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>4-12 mcg/ml</td>
<td>20-30 mcg/ml</td>
</tr>
<tr>
<td>Trough</td>
<td>&lt; 2 mcg/ml</td>
<td>&lt; 10 mcg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Volume of distribution (Vd)</th>
<th>0.25 L/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (Cl)</td>
<td>Normal renal function: ClCr</td>
</tr>
<tr>
<td></td>
<td>Functionally Anephric: 0.0043 L/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Surgically Anephric: 0.0021 L/kg/hr</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis: 1.8 L/hr</td>
</tr>
<tr>
<td>Half-life</td>
<td>Normal renal function: 2-3 hr</td>
</tr>
<tr>
<td></td>
<td>Functionally Anephric: 30-50 hr</td>
</tr>
<tr>
<td>Protein binding</td>
<td>20-30%</td>
</tr>
</tbody>
</table>

AG weight and renal function estimates

- Recent studies display improved PK estimates for AG in obese and underweight patients
  - Lean body weight better estimates Vd
  - Estimated glomerular filtration rate (eGFR) more accurately predicts AG CL than CrCl
- For this lecture IBW and CrCL will be used as examples

Aminoglycoside therapeutic C_max targets

- Traditional dosing
  - Tobramycin and Gentamicin
    - Severe infections – 8-10 mg/L
    - Moderate infections – 6-8 mg/L
    - Mild infections – 3-5 mg/L
  - Amikacin
    - Severe infections – 25-30 mg/L
    - Moderate infections – 22-25 mg/L
    - Mild infections – 20-22 mg/L
- Extended interval or once-daily dosing
  - C_max not determined, doses based on levels 6-14 hours after dose

Aminoglycoside Peak/MIC Ratio

Extrapolating True Peaks and Troughs

\[ \text{True peak} = \frac{C_{\text{max}}}{e^{\frac{t}{t_1}}} \]

\[ \text{True trough} = C_{\text{min}} \times e^{\frac{-t_t}{t_1}} \]

1 = time between actual draw time and administered dose
**Initiating a dosing regimen**

- Specific patient information
  - Height/Weight
  - Age
  - Gender
  - Serum creatinine
  - Infection type
  - Pathogen
  - Coexisting conditions

**Dose initiation**

i.e. “Patient has not received aminoglycosides before and we have no patient-specific values to work with”

- To estimate $k$ (in hr$^{-1}$)

$$k = \frac{0.00293 \times (\text{CrCl})}{1 + 0.014}$$

- Initial dosing interval

$$\tau = \frac{(C_{\text{max}} - C_{\text{min}})}{k}$$

- Initial dosing

$$\text{Dose} = \frac{T \times (V_d) \times (C_{\text{min}})}{1 - e^{-\frac{T}{\tau}}}$$

**Aminoglycoside Case #1**

- 45 year old male with *P. aeruginosa* intra-abdominal infection sensitive only to gentamicin
  - Height 75 inches
  - Weight 84.5 kg
  - SCr = 1.2 ml/min
  - Infusion time 0.5 h

- Calculate starting dose and interval

**Aminoglycoside Case #2 - adjusting doses**

A 33 year old male is admitted with significant burn injuries. Along with fluid supplementation, he is started on tobramycin to treat an extensive infection contracted during his stay. Height 70 inches; Weight 82 kg; SCr 0.7 mg/dL.

Tobramycin was dosed at 150 mg every 8 hours. On the third dose the following levels were obtained: $C_{\text{max}}$ 6 (@ 0900) and $C_{\text{min}}$ 1.8 (@1600).

- Calculate tobramycin $k$ and Vd in this patient

**Aminoglycoside calculations**

1. CrCl

\[ \text{93 ml/min} \]

2. $k$ (hr$^{-1}$)

\[ \frac{0.00293 \times (\text{CrCl})}{1 + 0.014} = 0.29 \text{ hr}^{-1} \]

3. $V_d = 0.25 \text{ L/kg}$

\[ \frac{93}{70} = 21 \text{ L} \]

\[ \frac{1.2}{70} = 0.017 \text{ hr}^{-1} \]

\[ \text{Dosing interval} = \frac{T \times (V_d) \times (C_{\text{min}})}{1 - e^{-\frac{T}{\tau}}} = 8.44 \text{ hr or 8 h} \]

\[ \text{Dose} = 200 \text{ mg every 8 h} \]

\[ \text{205 or 200 mg} \]

**Aminoglycoside Case #2 - adjusting doses**

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- Calculate tobramycin $k$ and Vd in this patient

$$k = \frac{C_{\text{max}}}{C_{\text{min}}}$$

$$V_d = \frac{(P_d) 	imes (1 - e^{-kT})}{k \times (C_{\text{max}} - C_{\text{min}} \times (e^{-kT}))}$$

$$= 0.17 \text{ hr}^{-1}$$

$$= 33.1 \text{ L}$$
Dose adjustments
The C_{max} level of 6 mg/L is below the targeted peak for this patient.
1. Calculate a new dose to achieve a peak of 10 mg/L

\[
\text{Maintenance dose} = \frac{T \times (k) \times (V_d) \times (C_{\text{max}})}{1 - e^{-\frac{1}{T \times k} (1 - e^{-\frac{1}{T \times k}})}}
\]

2. What is the estimated trough with this new dose? Is it acceptable?

\[
k = \frac{\ln(C_{\text{trough}})}{\text{time between samples}}
\]

3. What if your dosing interval was 12 hours instead of 8h?

\[
\frac{0.17 \text{ hr}^{-1}}{33.1 \text{ L}} = 260 \text{ mg} \approx 250 \text{ mg}
\]

\[
\frac{0.17 \text{ hr}^{-1}}{33.1 \text{ L}} = 3.1 \text{ mg/L}
\]

Once-Daily Aminoglycosides
- Over 10,000 patients receiving once-daily aminoglycosides have been evaluated.
- Infections studied include: bacteremia, intra-abdominal infections, urinary tract infections, pneumonia and febrile neutropenic patients.
- No difference in efficacy has been reported to date.
- Some investigations have reported less nephrotoxicity for patients receiving once-daily aminoglycosides.

Extended Interval Dosing
- Concept
  - Increase peak/MIC ratio with larger doses
  - Longer interval between doses (ex. from 8h to 24h)
- Rationale
  - Utilize the concentration dependent effect for increased efficacy
  - Minimize toxicity with lower trough concentration between doses

Extended Interval Dosing
- Dose
  - Gentamicin or tobramycin 5-7 mg/kg
  - Amikacin 15 mg/kg
- Interval

<table>
<thead>
<tr>
<th>Creatinine Cl</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60 ml/min</td>
<td>q24h</td>
</tr>
<tr>
<td>40-59 ml/min</td>
<td>q36 h</td>
</tr>
<tr>
<td>20-39 ml/min</td>
<td>q48 h</td>
</tr>
<tr>
<td>&lt; 20 ml/min</td>
<td>N/A</td>
</tr>
</tbody>
</table>
- Level obtained 6-14 hr after start of infusion
- Dose adjust and recheck level every 7 days

Extended Interval Dosing (Hartford Nomogram)

Nicolau et al. AAC 1995;39:650-655
**Probability of Toxicity by Cumulative AUC**

Probability of toxicity by cumulative AUC

- EIA Group
- TDA Group

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**Limitations of extended interval dosing**

- Populations not studied and therefore should not be used:
  - Pediatrics
  - Pregnancy
  - Burn patients
  - Ascites
  - CrCl < 20 ml/min
  - Dialysis

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**Vancomycin**

- Glycopeptide antibiotic and primary MRSA agent
- Concentration independent antibiotic
- Slowly bactericidal
- Toxicities historically associated with impurities in the drug formulation
  - "Mississippi mud"
  - Renal, ototoxicity
  - Improved synthesis has removed impurities
- Efficacy linked to AUC profile
- Vancomycin resistant MRSA now reported

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**Vancomycin Use and Monitoring Guidelines**

- Daily doses of 15-20 mg/kg (actual weight) every 8-12 h recommended for most patients with normal renal function
  - Loading doses of 25-30 mg/kg may be used
  - Vancomycin AUC/MIC ≥ 400 not attainable if
    - MIC ≥ 2 mg/L
  - Continuous infusion unlikely to improve outcome
- Monitoring trough concentrations
  - Maintain ≥ 10 mg/L
  - For MIC≥1 mg/L concentrations ≥ 15 mg/L for target AUC/MIC 400
  - Troughs 15-20 mg/L may improve penetration
- **Nephrotoxicity** = 2-3 consecutive increases in Scr (increase of 0.5 mg/dL or a >50% increase from baseline, whichever is greater)

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**Comparison of Vancomycin days to eradication for MRSA pneumonia**

- AUC/MIC <400
- AUC/MIC >400

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**AUC/MIC target in bacteremia**

- AUC/MIC > 373 was a greater predictor of MRSA bacteremia mortality than AUC/MIC > 400

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Vancomycin Key Parameters

Therapeutic plasma concentration
- Peak: 35-50 mcg/ml
- Trough: 10-20 mcg/ml

Bioavailability (F)
- <5%

Volume of distribution (Vd)
- 0.7 L/kg

Clearance (L/hr)
- Clearance adjusted for TBW (L/h)

Elimination rate constant (k)
- Cl/Vd in hr⁻¹

Half-life
- 6-8 hr

Protein binding
- 45-55%

AUC (mg/L*h)
- Dose/Cl

Vancomycin population derived doses

<table>
<thead>
<tr>
<th>Vancomycin dose</th>
<th>Creatinine Clearance</th>
<th>Interval</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg</td>
<td>&gt; 50 ml/min</td>
<td>q8-12h</td>
<td>trough*</td>
</tr>
<tr>
<td>15 mg/kg</td>
<td>50-30 ml/min</td>
<td>q24h</td>
<td>trough*</td>
</tr>
<tr>
<td>15 mg/kg</td>
<td>&lt; 10 ml/min; HD/PO</td>
<td>x 1</td>
<td>random</td>
</tr>
</tbody>
</table>

*obtained at steady state -- usually after third dose

Vancomycin population derived doses

Estimated Parameters Nomogram Dosing

Always use caution with vancomycin nomograms

In 200 patients, 58% achieved trough goals within 15-20 g/L

Should we monitor vancomycin routinely?

- Historically a standard of practice
- No definitive studies (i.e. prospective, randomized) to demonstrate benefit
- Can we extrapolate study findings to all patients?
- What about dosing adjustments and therapeutic goals?

When to Monitor

- Criteria
  - No peak concentrations necessary
  - Trough monitoring in patients with
    - aggressive dosing
    - high risk of nephrotoxicity
    - unstable renal function
    - Prolonged courses of therapy
- Frequency
  - > 1 trough prior to 4th dose not recommended for short course/low intensity
  - Prolonged course: at least 1 steady state trough
  - Aggressive dosing: once weekly if stable, more frequent otherwise
Adjusting the dose after levels

- **Linear PK principles**

\[
D_\text{opt} = \left(\frac{D_\text{opt}}{C_{\text{min}, \text{opt}}}ight) 
\]

Two types of “general” scenarios

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<thead>
<tr>
<th>Adjustment</th>
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<tbody>
<tr>
<td>1. Cmin excessively low/high</td>
<td>X ≤ 0.5 or ≥ 1.5 x target</td>
</tr>
<tr>
<td>2. Cmin slightly low/high</td>
<td>X slightly = within 0.5-1.5 x target</td>
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**Case #1**

A 62 year old female in respiratory failure is on a ventilator for the past week and develops MRSA VAP. Weight 65 kg, height 62 inches, BUN/Scr 26/1.2 The MIC of the pathogen to vancomycin is 1 mg/L.

What pharmacodynamic parameter should be targeted in this case?

a. Peak/MIC 50  
b. AUC/MIC 400  
c. Trough/MIC 10  
d. Daily dose/MIC 2000

**Case #1 - continued**

Recommend a dose to achieve this parameter.

a. 1000 mg every 24 h  
b. 1000 g every 12 hours  
c. 1000 mg every 8 hours  
d. 1500 mg x 1  
e. 1500 mg every 8 hours

**Case #2**

A 55 year old male with MRSA osteomyelitis is given vancomycin 1 g every 12 hours with a goal trough of 20 mg/L. He weighs 105 kg and has a CrCl 75 ml/min. The vancomycin trough at Cmin is 8 mg/L. The physician treating this patient turns to you for recommendations.

**Clearance (L/hr)**

\[
[0.695](\text{CrCl} \times \text{TBW/IBW}) + 0.05 \times 0.06 
\]

2.1 L/hr

**AUC (mg/L•hr)**

Target AUC / MIC goal is 400  
400 / 1 = 400  
AUC = Daily dose / Clearance  
400 = Daily dose / 2.1 L/hr  
Daily dose = 840 mg

(Note, because the calculated dose is not an orderable quantity, either 750mg or 1000mg every 24 h is acceptable.)
Case #2

A 55 year old male with MRSA osteomyelitis is given vancomycin 1 g every 12 hours with a goal trough of 20 mg/L. He weighs 105 kg and has a CrCl 75 ml/min. The vancomycin trough at C<sub>ss</sub> is 8 mg/L. The physician treating this patient turns to you for recommendations.

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<tbody>
<tr>
<td>1. C&lt;sub&gt;ss&lt;/sub&gt; excessively low/high excessive = ≤ 0.5 or ≥ 1.5 x target</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2. C&lt;sub&gt;ss&lt;/sub&gt; slightly low/high slightly = within 0.5-1.5 x target</td>
<td>X</td>
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Case 2 update

A week later, the patient receives IV contrast which results in minor renal impairment CrCl 40 ml/min. The new trough with your recommended dose is now 26 mg/L. Again you are consulted for your recommendations.

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Runs a 5,000 patient Monte Carlo simulation based on your patient’s demographic parameters to predict the likelihood of target attainment for different dosing regimens!