Vancomycin Basic Pharmacokinetics

Liberation and Absorption - negligible


- Measurable
  - Protein Binding 30-55%
  - Tissue Penetration - good
  - Lipid Solubility – Yes, but does not penetrate into normal CSF

Vancomycin Metabolism - Negligible

Vancomycin Elimination and Distribution

- Volume of Distribution
  \[ V_c = 0.15 \text{ L/Kg} \]
  \[ V_{ss} = 0.5 - 0.9 \text{ L/Kg} \]

- Elimination Half-lives
  \[ \text{Alpha} = 7 \text{ minutes} \quad \text{Beta} = 0.4 \text{ hours} \quad \text{Gamma} = 3-9 \text{ hours} \]


How do we measure it?

FPI – Florescence Polarization Immunoassay or EMIT® – Enzyme Multiplied Immunoassay

When do we do it? - *(Chapter 15, pp 336)*

- When we reach steady state – 5 half-lives ~ around the fourth dose.
- When distribution is complete – about one hour after the infusion stops.

Optimum sampling times.
- Trough within 30 minutes of a scheduled dose.
- *Dose \leq 1.25 \text{ g infuse over 90 minutes.}*
- *Dose 1.5 - 2 \text{ g infuse over 120 minutes.}*
- Peak 60 minutes after the infusion stops.

Predicting Steady Levels

- Target Concentrations
  - Peak 30-40 mg/L
  - Trough 10-20 mg/L
Prospectively (Population Pharmacokinetic Estimates)

\[
\text{CrCl (ml/min)} = \frac{(140-\text{Age}) \cdot \text{CrClWt}}{72 \cdot \text{SrCr}} \cdot (0.85 + \text{Sex} \cdot 0.15) \quad \text{where Sex = 1 for a male and 0 for a female.}
\]


Modified \[\text{CrCl (ml/min)} = \frac{(140-\text{Age}) \cdot \text{CrClWt}}{73 \cdot (\text{SrCr} + 0.07)} \cdot (0.85 + \text{Sex} \cdot 0.15) \text{ where Sex=1 for a male and 0 for a female.} \]

IBW (males)

50 Kg + 2.3 Kg/inch over 5 feet

IBW (females)

45.5 Kg + 2.3 Kg/inch over 5 feet

\[\text{BMI} = \frac{\text{Wt (Kg)}}{(\text{Ht (In)} \times 0.0254)^2} \]

\[\text{CorrSrCr} = \frac{\text{SrCr} + 0.07}{0.987} \]

Ann Pharmacother 2011;45:748-56.

If BMI is > 25 Kg/m\(^2\), then \(\text{CrClWt} = \text{IBW} + 0.4 \times (\text{ActBW} - \text{IBW})\)

If ActBW > IBW and BMI \(\leq 25\) \(\text{CrClWt} = \text{IBW}\)

If ActBW < IBW, then \(\text{CrClWt} = \text{ActBW}\)


TR Only: \[\left(\frac{\text{Dose}}{\text{Tau}}\right)_{\text{new}} = \left(\frac{\text{Dose}}{\text{Tau}}\right)_{\text{current}} \cdot \frac{C_{\text{desired}}}{C_{\text{measured}}} \quad \text{[C_{\text{desired}} = Target 15 mg/L]} \]


1. Calculate the elimination rate constant.

\[k_e = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} \]

\[k_e = \frac{\ln C_{pk} - \ln C_{ir}}{t_{tr} - t_{pk}} \]

\[\ln C_{pk} / C_{ir} = \ln \left(\frac{C_{pk}}{C_{ir}}\right) \]

2. Calculate \(C_0\) (\(t_{pk}\) = elapsed time from start of infusion)

\[C_0 = \frac{C_{pk}}{e^{-k_e(t_{pk} - t_{0})}} \]

3. Calculate the half-life.

\[t_{1/2} = \frac{\ln 2}{k_e} \]

4. Calculate the volume of distribution.

\[V_s = \frac{R_i}{k_e} \cdot \frac{1-e^{-k_e t_{aul}}}{C_0 - C_t \cdot e^{-k_e t_{aul}}} \]

5. Calculate the dosing interval.

\[\tau = \frac{\ln \left(\frac{C_{\text{Max,desired}}}{C_{\text{Min,desired}}}\right)}{k_e} + t_{inf} \]

6. Calculate the new infusion rate.

\[R_i = C_{\text{Max,desired}} \cdot k_e \cdot V_s \cdot \frac{\left(1-e^{-k_e \tau}\right)}{\left(1-e^{-k_e t_{aul}}\right)} \]

7. Calculate the new peak.

\[C_{ss, pk} = \frac{R_i}{V_s \cdot k_e} \cdot \frac{\left(1-e^{-k_e \tau}\right)}{\left(1-e^{-k_e t_{aul}}\right)} \]

8. Calculate the new trough.

\[C_{ss, tr} = C_{ss, pk} \cdot e^{-k_e (\tau-t_{aul})} \]
Aminoglycoside Basic Pharmacokinetics

Liberation and Absorption - Peak following IM administrations is 30-120 minutes after administration. Oral 0.3-15% of the oral dose is absorbed.

Distribution - (Chapter 14, pp 287)
- Measurable
- Protein Binding < 10%
- Tissue Penetration - Distributes well in body fluids; synovial, peritoneal, ascitic and pleural.
- Lipid Solubility - Poor: Does not penetrate into adipose tissue or normal CSF.

Metabolism - Only 5-15% Gyselynck et al, J Infect Dis 1971,S70-6.

Elimination and Distribution - (Chapter 14, pp 289-292)
- Volume of Distribution ($V_{ss}$)
  - Normal = 0.2-0.25 L/Kg
  - Dehydrated = 0.15 L/Kg and Overhydrated = 0.3 L/Kg
- Elimination Half-lives
  - Alpha = 5 minutes
  - Beta = 2-4 hours
  - Gamma = 100 hours

Pharmacodynamic Characteristics: (Chapter 16, pp 342-347)
- Concentration Effect Relationships.
  - Concentration Dependent Activity (Peak:MIC ratio or AUC:MIC ratio)
    - Activity is associated with high ratios.
  - Post-antibiotic Effect (PAE) – The persistent inhibitory effect of the antibiotic following its removal.

Toxicity Considerations: (Chapter 14, pp 293-298)
- Nephrotoxicity:
  - Generally reversible
  - Thought to be due to prolonged trough elevation > 2 mg/L
- Ototoxicity:
  - Often not reversible
  - May be due to elevated peaks, but data unclear

Two Dosing Approaches

Traditional (Multiple Dosing) Approach: (Chapter 14, p 306)
- Dose to achieve a target peak and trough concentration.

<table>
<thead>
<tr>
<th></th>
<th>Peak (mg/L)</th>
<th>Trough (mg/L)</th>
<th>Peak (Life Threatening infection)</th>
<th>Peak (Serious Infection)</th>
<th>Peak (Synergy/UTI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>6-10</td>
<td>1</td>
<td>8-10 mg/L</td>
<td>6-8 mg/L</td>
<td>4-6 mg/L</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>6-10</td>
<td>1</td>
<td>8-10 mg/L</td>
<td>6-8 mg/L</td>
<td>4-6 mg/L</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20-30</td>
<td>10</td>
<td>25-30 mg/L</td>
<td>20-25 mg/L</td>
<td>15-20 mg/L</td>
</tr>
</tbody>
</table>

Dosing intervals generally range from every 8 (good renal function) to 24 hours (poor renal function).
Extended Interval (Once Daily) Approach (Chapter 14, pp 304-305)

- Dose to optimize the peak:MIC ratio
  - Approximately 10:1 to 20:1
- Dosing interval is usually every 24 hours
- Thought to reduce toxicity

Multiple Dosing Regimen Concentrations

- When we reach steady state: 5 half-lives ~ around the third dose.
- When distribution is complete: 30 minutes after the infusion is complete.
- Length of infusion: 30 minutes
- Optimum sampling times:
  - Trough within 30 minutes of a scheduled dose.
  - Peak 30 minutes after the infusion stops.

Extended Interval Regimen Concentration

- Infusion length: 60 minutes.
- Sampling time: Collect a single sample 6-14 hours after the initial dose.

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Dose (Adults):</strong> 5-7 mg/Kg</td>
</tr>
<tr>
<td><strong>Initial Dosing and Interval (Adults):</strong></td>
</tr>
<tr>
<td>$Cl_{cr} &gt; 60$ ml/min</td>
</tr>
<tr>
<td>$Cl_{cr} \leq 60$ ml/min</td>
</tr>
<tr>
<td><strong>Initial Dosing and Interval (Pediatrics):</strong></td>
</tr>
<tr>
<td>3 mo. – 2 years</td>
</tr>
<tr>
<td>2 – 8 years</td>
</tr>
<tr>
<td>&gt; 8 years</td>
</tr>
</tbody>
</table>


Dosage Adjustment:

- According to the nomogram.
Selected References


44. Van Lent-Evers NAE, Mathot RAA, Geus WP, Van Hout BA, Vinks AAT. Impact of Goal-Oriented and Model-Based Clinical Pharmacokinetic Dosing of Aminoglycosides on Clinical Outcome: A Cost-Effectiveness Analysis. Ther Drug Monit ; 1999; 21(1):63-73. (IDIS Article 420768)


