Optimizing therapy with glycopeptides and aminoglycosides

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Antibiotic Goals

- Promote bacteria death
- Prevent the emergence of resistance
- Avoid toxicity

Antibiotic must not only attach to target but must occupy an adequate number of binding sites during a certain time.

That depends on drug concentration and time within the organism – the PK, and also on bacteria susceptibility – MIC.

Usually antibiotic concentration must be over 3-5 times MIC.

Underdosing

- Increase in Volume of distribution
- Increase in clearance
Patterns of Antimicrobial Activity

Concentration

\[ C_{\text{max}} \]

Mainly dependent of VD

Aminoglycosides

Metronidazol

Area under the concentration curve

Azithromycin

Fluoroquinolones

Glycopeptides

Mainly dependent of the Cl

Beta-lactams

Carbapenems

T>MIC

MIC

Time (hours)
Concentration and Volume of Distribution

- The apparent volume of distribution indicates into how large a volume the drug distributes if it were at the same concentration as that in plasma.

- Initial peak concentration is only dependent on dose and volume of distribution.

- Clearance indicates how much fluid is cleared of the drug per time.
Individual variation

Pharmacokinetics of antibiotics for a given population
Volume of Distribution

- Intracellular
- Extracellular

Volume Resuscitation

Hidrophilic Drugs

Lipophilic Drugs
Fast bactericidal activity depends on peak drug concentration

Slower and independent of drug concentration (postantibiotic effect)

Aminoglycosides antimicrobial activity

Concentration (mg/L)

Baral Am J Med.2003;114:194
90% probability of resolution by day 7 if a Cmax/MIC of ≥ 10 is achieved within the first 48h of aminoglycoside therapy

Kashuba Antimicrob Agents Chemother 1999

Moore J Infect Dis 1987;155. 93
Meta-analysis of 21 randomised trials; N=3091

- Multiple doses or large dose
- Large dose associated with a non-significant decrease in antibiotics failures (especially in Pseudomonas)

- Large dose administration reduced the risk of nephrotoxicity (fixed effects risk ratio 0.74 (0.54 to 1.00)).

- There was no significant difference in ototoxicity between the two dosing regimens, but the power of the pooled trials to detect a meaningful difference was low.

- There was no significant difference in mortality

Barza M BMJ 1996;312:338
Pharmacokinetics / Pharmacodynamics

First dose of Aminoglycosides

**Gentamicin**

- 7.4mg/kg. Peak target 16 mg/L
- N=32; Vd=0.41l/kg

**Amikacin**

- 25mg/kg. Peak target 64 mg/L
- N=74; Vd=0.41l/kg

No relationship with age, organ failure, SOFA or sepsis severity
Pharmacokinetics / Pharmacodynamics

First dose of Aminoglycosides

Vd first dose 0.41 l/kg (±0.1)

Gonçalves-Pereira Clin Microbiol Infect 2010;16:1258


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Frail</th>
<th>Non frail</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (l)</td>
<td>14.8 ± 1.4</td>
<td>15.2 ± 2.2</td>
<td>0.56 (NS)</td>
</tr>
<tr>
<td>CL (ml min⁻¹)</td>
<td>46.6 ± 10.7</td>
<td>58.2 ± 12.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Aminoglycosides Pharmacokinetics

Pharmacodynamic parameter of efficacy: Peak/MIC
Toxicity (Renal accumulation): Trough concentration and interval

Pharmacokinetics / Pharmacodynamics

- Pharmacodynamic parameter of efficacy: Peak/MIC
- Toxicity (Renal accumulation): Trough concentration and interval

Renal proximal convoluted tubules; a saturable process
Renal failure

Concentration vs. Time (hours)
Optimization of Aminoglycoside Therapy

G. L. Drusano* and Arnold Louie

Aminoglycosides are experiencing a resurgence in use because of the spread of multiresistant Gram-negative pathogens. Use of these agents is attended by the occurrence of nephrotoxicity. Aminoglycoside optimization of dose can be defined as the dose having the highest likelihood of a good outcome and the lowest likelihood of toxicity. We have defined the metric \( \Delta \) as the difference between the likelihoods of good outcome and toxicity, with higher values being better. We developed a method for explicitly evaluating \( \Delta \) for different daily doses of drug and different scheduling of administration every 12 hours cannot attain a high enough likelihood. Daily administration of more acceptable probability leads to better identification of the phenomenon. For identified, optimal dosing regimens, we provided a summary for aminoglycosides requiring prolonged exposure and toxicity. For Aminoglycosides requiring prolonged exposure and toxicity.

### TABLE 2. Optimization of empirical aminoglycoside therapy with administration daily

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>MIC (mg/liter)</th>
<th>Probability of effect</th>
<th>Probability of toxicity</th>
<th>( \Delta )</th>
<th>AUC(_{0-24}) (mg · h/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>4.0</td>
<td>79.7 ± 0.086</td>
<td>0.912 ( \times ) 10(^{-4} ) ± 0.908 ( \times ) 10(^{-2} )</td>
<td>79.7 ± 8.61</td>
<td>192 ± 67.6</td>
</tr>
</tbody>
</table>
Dose of antibiotics

Aminoglycosides

• Normalization of the increase in Vd and Cl (with sepsis resolution)

• High antibiotic concentration

Use of TDM – Peak and a second measurement between 16-20h
Linear PK and 1st order kinetics

480mg. Peak (1h) – 18mg/dl; Trough (17h) 2mg/dl Vd=24,1L Cl=3,3ml/min

Recommended dose 480mg after 28h
Peak (2h) – 18mg/dl; Trough (16h) 2mg/dl Vd=20,3 Cl=3,2ml/min

Recommended dose 400mg after 27h

Progressive normalization of PK

<table>
<thead>
<tr>
<th></th>
<th>2nd day</th>
<th>7th day</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak concentration (µg/ml)</td>
<td>4.9 ± 1.2</td>
<td>6.8 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Trough concentration (µg/ml)</td>
<td>1.17 ± 0.65</td>
<td>1.10 ± 0.3</td>
<td>ns</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>0.43 ± 0.12</td>
<td>0.29 ± 0.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>T (1/2 h)</td>
<td>4.3 ± 2.0</td>
<td>3.2 ± 0.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cl (l/kg/h)</td>
<td>0.07 ± 0.02</td>
<td>0.05 ± 0.01</td>
<td>ns</td>
</tr>
<tr>
<td>TDR (mg/kg/h)</td>
<td>5.14 ± 2.43</td>
<td>3.98 ± 1.67</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Dose of antibiotics**

**Vancomycin**

- **Clinically evaluable patients (n=53)**
  - AUC/MIC ≤345 (n=21)
    - 24% success
  - AUC/MIC >345 (n=32)
    - 78% success

- **AUIC <400**
- **AUIC >400**

**Clinically evaluable patients**

- **AUC/MIC >345 (n=32)**
  - 78% success

**AUC/MIC ≤345 (n=21)**
- 24% success

*Moise P. Am J Health Syst Pharm 2000;57 (Suppl 2):S4–S9*
Dose of antibiotics

**Vancomycin**

- To achieve therapeutic concentrations rapidly loading doses are recommended
- Recommend giving high end of normal loading dose (or even higher dose)
  - Example: Vancomycin (normal patient Vd ~0.7 L/kg)
    - 100 kg septic shock patient

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Estimated Vd</th>
<th>Estimated Peak level (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg/kg ABW</td>
<td>~1 L/kg due to fluid resuscitation</td>
<td>25</td>
</tr>
</tbody>
</table>

**Results**—Data were collected on a random sampling of 421 patients, stratified by body mass index, who met the inclusion criteria. Most patients in each body mass index category received a fixed dose of vancomycin 2 grams daily divided into two doses (underweight 82%, normal weight 90%, overweight 86%, obese 91%). Adequate initial dosing (≥ 10 mg/kg/dose) was achieved for 100% of underweight, 99% of normal weight, 93.9% of overweight, and 27.7% of obese patients (p < 0.0001).

### PK monitoring – Vancomycin

<table>
<thead>
<tr>
<th>N</th>
<th>Vd (L)</th>
<th>Vol (L)</th>
<th>Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>75 (81)</td>
<td>49</td>
<td>53.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>Cl (L/H)</th>
<th>Vol (L/H)</th>
<th>Increase</th>
<th>Cr Cl (L/H)</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>3.6 (3.9)</td>
<td>3.6</td>
<td>0</td>
<td>84 (46)</td>
<td>9</td>
</tr>
</tbody>
</table>

#### Continuous Infusion (N=25) vs. Intermittent (N=18)

<table>
<thead>
<tr>
<th></th>
<th>Continuous Infusion</th>
<th>Intermittent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trough</td>
<td>58% (Css&gt;20)</td>
<td>42% (&gt;15)</td>
</tr>
<tr>
<td>AUC/MIC&gt;400</td>
<td>88%</td>
<td>45%</td>
</tr>
<tr>
<td>Cure</td>
<td>70%</td>
<td>58%</td>
</tr>
</tbody>
</table>
Measured concentrations were more often in therapeutic range when guided by TDM then by Moellering’s nomogram.

### Out of Therapeutic Range

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak</td>
<td>A-50%</td>
<td>B-50%</td>
</tr>
<tr>
<td>Trough</td>
<td>A-0%</td>
<td>B-43.8%</td>
</tr>
<tr>
<td>Dose/kg</td>
<td>A – 19±0.5 mg</td>
<td>B – 17±0.4 mg</td>
</tr>
</tbody>
</table>

Vancomycin Dosing in Critically Ill Patients: Robust Methods for Improved Continuous-Infusion Regimens

Jason A. Roberts, Fabio Silvio Taccone, Andrew A. Udy, Jean-Louis Vincent, Frédérique Jacobs, and Jeffery Linman

Despite the development of novel antibiotics active against Gram-positive bacteria, vancomycin generally remains the first treatment, although rapidly achieving concentrations associated with maximal efficacy provides an unresolved challenge. The objective of this study was to conduct a population pharmacokinetic analysis of vancomycin in a large population of critically ill patients. This was a retrospective data collection of 206 adult septic critically ill patients who were administered vancomycin as a loading dose followed by continuous infusion. The concentration-versus-time data for vancomycin in serum was analyzed by a nonlinear mixed-effects modeling approach using NONMEM. Monte Carlo simulations were performed using the final covariate model. We found that the best population pharmacokinetic model consisted of a one-compartment linear model with combined proportional and additive residual unknown variability. The volume of distribution of vancomycin (1.5 liters/kg) was described by total body weight and clearance (4.6 liters/hr) by 24-hour urinary creatinine clearance (CrCl), normalized to body surface area. Simulation data showed that a 35 mg/kg loading dose was necessary to rapidly achieve vancomycin concentrations of 20 mg/liter. Daily vancomycin requirements were dependent on CrCl, such that a patient with a CrCl of 100 ml/min/1.73 m² would require at least 35 mg/kg per day by continuous infusion to maintain target concentrations. In conclusion, we have found that higher-than-recommended loading and daily doses of vancomycin seem to be necessary to rapidly achieve therapeutic serum concentrations in these patients.
Dose of antibiotics

Vancomycin

Vancomycin continuous infusion

\[
\text{Cl vanco (L/h)} = 0.021 \times \text{ClCr (8h) (mL/m)} + 2.3
\]

Perfusion Rate vanco (g/d) = Cl Vanco \times 0.6


Baptista ESICM 2013
Higher vancomycin doses and nephrotoxicity

Time to nephrotoxicity for patients treated with vancomycin

- Standard dose of vancomycin (n=220)
  - Vancomycin dose
    - C_{min}, µg/ml
      - Standard (<4 g/day): 9
      - High (≥4 g/day): 18

- High dose of vancomycin (n=26)

*Probability of remaining non-nephrotoxic

Days after initiation of therapy

*Nephrotoxicity: increase in creatinine ≥0.5 mg/dl

Lodise T Antimicrob Agents Chemother 2008;52:1330
Antibiotics Pharmacokinetics

Healthy

Organ Failure

Sepsis

Increased Vd

Decreased Cl

Gonçalves-Pereira. Crit Care 2011, 15:R206
Table 1—Broad Guidelines for Loading and Maintenance Dosing of Antibiotics in Critically Ill Patients With MODS

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Solubility</th>
<th>Main Organ Systems Responsible for Clearance</th>
<th>PD Parameter Associated With Maximal Activity</th>
<th>LD in Patients With Increased Vd</th>
<th>MD in Acute Kidney Injury</th>
<th>MD in Hepatic Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Lactams</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>$fT &gt; MIC$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Dose decreases preferred to increased time between intervals</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>$C_{\text{max}} / \text{MIC}$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Increased time intervals preferred to dose decreases, titrate dosing according to TDM results</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>Hydrophilic</td>
<td>Renal</td>
<td>$AUC_{0-24} / \text{MIC}$</td>
<td>Administer a high LD on day 1, as Vd will be significantly increased</td>
<td>Titrate dosing according to TDM results</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Lipophilic</td>
<td>Renal and hepatic (ciprofloxacin, moxifloxacin), renal (levofloxacin)</td>
<td>$AUC_{0-24} / \text{MIC}$ and $C_{\text{max}} / \text{MIC}$</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction and principal organ system responsible for clearance</td>
<td>Decrease dose based on the degree of organ dysfunction</td>
</tr>
<tr>
<td>Lincosamides</td>
<td>Lipophilic</td>
<td>Renal and hepatic</td>
<td>$AUC_{0-24} / \text{MIC}$ and $fT &gt; MIC$</td>
<td>Administer dosing for conserved organ function on day 1</td>
<td>Decrease dose based on the degree of organ dysfunction</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>$fT &gt; MIC$ and $AUC_{0-24} / \text{MIC}$</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Nitroimidazoles (metronidazole)</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>$C_{\text{max}} / \text{MIC}$</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Cyclic lipopeptides</td>
<td>Lipophilic and hydrophilic</td>
<td>Renal</td>
<td>$C_{\text{max}} / \text{MIC}$</td>
<td>Increase dosing interval</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
<tr>
<td>Glycyclines</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>$AUC_{0-24} / \text{MIC}$</td>
<td>Administer LD per product information</td>
<td>Normal dosing</td>
<td>Decrease dosing</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Lipophilic</td>
<td>Hepatic</td>
<td>$AUC_{0-24} / \text{MIC}$ and $fT &gt; MIC$</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
<td>Normal dosing</td>
</tr>
</tbody>
</table>

$AUC_{0-24} / \text{MIC}$ = area under the concentration curve over 0 to 24 h-to-minimum inhibitory concentration ratio; $C_{\text{max}} / \text{MIC}$ = peak concentration-to-minimum inhibitory concentration ratio; $fT > MIC$ = time over the minimum inhibitory concentration; LD = front-loaded dose; MD = maintenance dose; MIC = minimum inhibitory concentration; MODS = multiple organ dysfunction syndrome; PD = pharmacodynamic; TDM = therapeutic drug monitoring; Vd = volume of distribution.

Uldemollins, Chest 2011; 139:1210
Approach to Dose during Hemofiltration

1. **Loading dose = desired concentration (table 1) \times Vd (table 3)**

2. Calculate CRRT clearance based on mode of CRRT, formulae in text and values from table 3

3. Total clearance \( C_{\text{tot}} \) = calculated CRRT clearance + non-CRRT clearance

4. **Pharmacokinetic target?**
   - \( C_{\text{max}} \):MIC and \( AUC_{24} : \text{MIC} \)

5. Calculate target mean concentration = target \( AUC_{24} / 24 \)

6. Calculate dosing interval = dose/(Cp \times C_{\text{tot}})

7. Repeat loading dose at calculated dosing interval

8. **Repeat loading dose at calculated time**

9. **Time above threshold concentration**

10. **Maintenance infusion rate = elimination rate**

11. **Calculate half-life = 0.693 \times Vd/C_{\text{tot}}**

12. Calculate time to reach target trough concentration

Approach to Dose during Hemodialysis

Aminoglycosides

Conclusions: In clinical situations where gentamicin is used as the primary therapy in a patient receiving hemodialysis with a CAHP hemodialyzer, conventional doses after each dialysis session are not as efficient at achieving treatment targets as predialysis dosing with larger doses.

An expert is someone who has stop thinking. He knows...

Frank Lloyd Wright