Current vancomycin dosing recommendations for pediatric patients: a pharmacokinetic evaluation

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Vancomycin

- First-line treatment for suspected MRSA infections in neutropenic children
- Few pediatric pharmacokinetic data available
- AUC/MIC is preferred parameter
- Current dose regimens appear insufficient to obtain AUC/MIC ≥ 400
- Vancomycin clearance increased in hematology-oncology patients

Le et al. Pediatr Infect Dis J 2013
Initial dose regimen in UZ Brussel: 15mg/kg 4 times daily, adjusted afterwards according to trough levels.

However:

- Initial trough levels far too low
- Several days (up to 1 week) often needed to obtain adequate trough levels
Research questions

- Influential factors on vancomycin clearance, trough levels and AUC/MIC in pediatric patients?
- Doses needed for therapeutic trough level and AUC/MIC ≥ 400?
- “Normal” pediatric patient vs. hematology/oncology: different dose needed for AUC/MIC ≥ 400?
Methods

- Retrospective study: 2011-2013

- Inclusion criteria
  - Intermittent vancomycin infusion
  - Dose frequency: 4 times daily
  - Patient age: > 1 y and < 18 y
  - Steady state (≥ 4 doses)

- Data collected from electronic patient files
  - Vancomycin dose, frequency, infusion time, trough levels
  - Age, gender, weight, length
  - Diagnosis, comorbidities
  - Serum creatinin values available
  - ≥ 2 trough values available
  - Not on intensive care
  - Creatinin clearance, administered fluids, (nephrotoxic) co-medication
Methods

- One-compartment first-order model with Bayesian analysis: simulation possible when only trough levels available
- PK software: JPKD (JavaPK for Desktop), Kaoshiung Medical University Taiwan

- Input: gender, body weight, body length, VANC dose, dosing interval, infusion time, serum creatinin, trough value
- Output: Volume of distribution, vancomycin clearance

Wrisko et al. Ther Drug Monit 2000
Methods

- Renal clearance: Schwartz equation
- MIC = 1 mg/L (conservative approach)
- Adequate trough levels: 10-20mg/L
- Patients stratified according age: < 6 year, 6 -12 year, > 12 year
Results

- 24 patients (21 hematology/oncology) → 183 trough levels available for analysis
- Patient characteristics

<table>
<thead>
<tr>
<th>Patient variables (N=24)</th>
<th>Median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>6.3 (range 1 - 15)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>15/9</td>
</tr>
<tr>
<td>Hematological/oncological malignancy</td>
<td>21</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>19.98 (16.35 - 43.00)</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>114.50 (102.60 - 156.00)</td>
</tr>
<tr>
<td>Serum creatinin (mg/dL)</td>
<td>0.38 (0.30 - 0.45)</td>
</tr>
<tr>
<td>VANC trough level (mg/L)</td>
<td>10.13 (7.14 - 13.54)</td>
</tr>
<tr>
<td>Vancomycin clearance (L/hr/kg)</td>
<td>0.186 (0.14 - 0.24)</td>
</tr>
<tr>
<td>Creatinin clearance (ml/min/1.73m²)</td>
<td>195.08 (156.58 - 244.44)</td>
</tr>
<tr>
<td>VANC distribution volume (L/kg)</td>
<td>1.08 (1.06 - 1.11)</td>
</tr>
</tbody>
</table>
Results

- **Vancomycin clearance: univariate analysis**

  ![](image1.png)  
  ![Image 1](image2.png)  
  ![Image 3](image3.png)

  **Significant correlations with:**
  - Weight
  - Fluids
  - Age
Results

- Overall impact of age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of patients</th>
<th>Median VANC clearance (L/h/kg)</th>
<th>Median dose (mg/kg)</th>
<th>Median trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6</td>
<td>9</td>
<td>0.2260</td>
<td>24.31</td>
<td>9.89</td>
</tr>
<tr>
<td>6 -12</td>
<td>11</td>
<td>0.2071</td>
<td>18.38</td>
<td>10.55</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>4</td>
<td>0.1350</td>
<td>13.95</td>
<td>11.41</td>
</tr>
</tbody>
</table>

- Agreement between AUC/MIC and trough levels: 86% (PPV: 80%)

<table>
<thead>
<tr>
<th>AUC/MIC</th>
<th>Trough level (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10</td>
</tr>
<tr>
<td>&lt; 400</td>
<td>85.4% (70)</td>
</tr>
<tr>
<td>≥ 400</td>
<td>14.6% (12)</td>
</tr>
</tbody>
</table>
Results

Median dose needed for trough levels 10-20mg/L per age group

- <6y: 24.89 mg/kg (19.55 - 29.69)
- 6-12y: 20.83 mg/kg (17.50 - 27.08)
- >12y: 13.95 mg/kg (13.54 - 13.95)

Median dose needed for AUC/MIC ≥ 400 per age group

- <6y: 29.36 mg/kg (23.96 - 39.90)
- 6-12y: 21.52 mg/kg (17.63 - 27.08)
- >12y: 13.95 mg/kg (13.54 - 14.71)
Results

- Different dose needed for hematology-oncology patients?

For AUC/MIC ≥ 400

- No malignancy: median dose 18.12 mg/kg QDS
- Malignancy: median dose 21.63 mg/kg QDS
Discussion & conclusion

- Current VANC dose regimen insufficient for our patients
- Age, weight, administered fluids affect VANC clearance
- Therapeutic trough levels + AUC/MIC≥400: significant differences between age groups
- Possible dosing algorithm
  - < 6 year: 25 – 30 mg/kg QDS
  - 6 - 12 year: 20 mg/kg QDS
  - > 12 year: 15 mg/kg QDS

*Only in case of malignancy?*

Sanders Pharmaceutisch Weekblad 2012
Cardoso Braz J Infect Dis 2012
Discussion & conclusion

- Limitations
  - Small population
  - No data on clinical outcome
  - Data imbalance between patients
  - AUC/MIC ≥ 400 & trough levels not validated for children

- Future
  - Prospective study
  - Additional focus on toxicity
  - Larger patient population
  - Clinical outcome
  - Both peak and trough levels