Latest issues in PK/PD of vancomycin

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Independence Maroc

Marriage Grace Kelly of Monaco

Suez crisis

Beginning of Cuban revolution

Hungarian revolution against Soviet
Independence Maroc

Marriage Grace Kelly of Monaco

Suez crisis

Hungarian revolution against Sovjet

Beginning of Cuban revolution

1956
• **Pharmacokinetics (PK):**
  = all the way the body manipulates the drugs
  1. Absorption
  2. Distribution
  3. Metabolism
  4. Elimination

• **Pharmacodynamics (PD):**
  = biochemical and physiological effects of a drug and its mechanism of action

• **PK/PD of vancomycin:**
  = the quantitative relation between pharmacokinetic parameters and microbiological parameters used to predict the effect
Can optimization of vancomycin dosing improve outcome (mortality and morbidity)?
HOST + BACTERIA = INFECTION
INFECTION + ANTIBIOTIC = CURED HOST
HOST FACTORS

PK of AB

Immune system

inadequate immunity

Excessive immunity

immunity

HEALTH

Infectious Diseases

Autoimmune Diseases
BACTERIAL FACTORS

**Virulence factors**

**Susceptibility: MIC**
ANTIBIOTIC FACTORS

PD of AB

Mechanism of action

- Cell wall synthesis
  - Cycloserine
  - Vancomycin
  - Bacitracin
  - Fosfomycin
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems

- Folic acid metabolism
  - Trimethoprim
  - Sulphonamides

- PABA
- DNA replication (DNA gyrase)
  - Nalidixic acid
  - Quinolones
- DNA-dependent RNA polymerase
  - Rifampin

- Protein synthesis (30S inhibitors)
  - Erythromycin
  - Chloramphenicol
  - Clindamycin
- Protein synthesis (50S inhibitors)
  - Tetracycline
  - Spectinomycin
  - Streptomycin
  - Gentamicin, tobramycin, amikacin
1. Pharmacokinetics of vancomycin (PK)

- Dosing & Elimination
- Serum concentrations Varying over time
- Concentrations in non-target tissues
- Concentrations at the site of the infection
• Large molecule, only suitable for IV use (IM = too painful)
  
  Vandecasteele, JAC, 2013, 68, 743-748

• New data:
  Considerable oral absorption.
  – 85 pt C. diff, 117 samples
  – 68,2 % > 0,05 µg/ml
  – 17,6 % > 2,50 µg/ml
  – Risk: dose and duration
    Severe CID/ICU stay
    Renal failure

Petit, Pharmacotherapy, 2015, 35, 2, 119-126

Geraci, Proc Staff Meet Mayo Clin, 1956, 31, 564-582
Griffith, Antibiot Annu, 1956, 3, 619-622
Dosing & Elimination

1 - 2 - 3 compartment model

• Steady state $\rightarrow 5 \times T_{1/2}$

Polard, Ther Drug Monit, 1999, 21, 395-403

Dosing & Elimination

Steady State
- Attained after approximately four half-times
- Time to steady state independent of dosage

Maintenance dose

Loading dose
• **Need for loading dose:**
  15 – 35 mg/kg

**2015 systematic review:**
- Faster target (15 – 20 µg/ml) attainment in adults
- No good data in children
- No data on clinical and microbiological outcome

Readon, Ann Pharmacology, 2015, Eprint
Roberts, AAC, 2011, 55, 2704-2709
• **Infusion rate:**
  Maximum 15 mg/min

Red man (neck) syndrome:
✓ Cardiac depression and hypotension
✓ Diffuse redness
~ vancomycin induced histamine release

Garrelis, NEJM, 1985, 312, 245
Newfield, Ann Int Med, 1979, 91, 581
Rybak, Am J Health Syst Pharm, 2009, 66, 82-98
Dosing & Elimination

95% renal (glomerular filtration): ↓ with ↓CL\textsubscript{Cr}

5% non-renal metabolism: ↑ with ↓CL\textsubscript{Cr}

(vancomycin degradation products)

Linear correlation CL\textsubscript{Cr} and Cl\textsubscript{Van}.

1 study 1984, 56 ptln, among them 30 with CL\textsubscript{CR} < 10 ml/min (C & G)

Matzke, AAC, 1984, 25, 433-437
Kitzes-Cohen, 2000, Ther Drug Monitoring, 22, 661-667

*FIG. 3. Vancomycin clearance versus CL\textsubscript{CR} (r = 0.8807; y = 0.689 x + 3.66; n = 75).*
• Linear correlation $\text{CL}_{\text{Cr}}$ and $\text{Cl}_{\text{Van}}$

Also in hyper-filtration:

- ICU, sepsis and SIRS
  - Shimanato, Int Care Med, 2013, 1247-1251
  - Lin Wu, Ther Drug Mont, 2015, Eprint
  - Phharm, J Med Assoc Thai, 2014, 97, 11, 1209-1219
  - Roberts, AAC, 2011, 55, 2704-2709
  - Matzke, AAC, 1984, 25, 433-437

- Obesity
  - Adane, Pharmacotherapy, 2015, 35, 127-139
  - Matzke, AAC, 1984, 25, 433-437
Need to adapt maintenance dose to

**KIDNEY FUNCTION**

Effect $Cl_{Cr}$ (loading dose 35 mg/kg; Maintenance dose 35 mg/kg)

**BODY WEIGHT**

Effect **body weight** $Cl$ (loading dose 35 mg/kg; $Cl_{Cr}$ $Cl$ 100 ml/min/1.73m$^2$)

Roberts, AAC, 2011, 55, 2704-2709
Need to adapt dose to kidney function and body weight

Prediction vancomycin clearance according to method of estimation of $\text{Cl}_\text{Cr}$ used

- 78 elderly
- 25-75 percentile
- Significant different ($p=0.0071$)
Dosing & Elimination

• Correlation Trough – AUC$_{24}$

Ryback, Am Jhealth Syst Pharm 2009, 66, 82-98

Poor correlation, with up to 23% underestimation AUC
- 3 historical data sets, 47 patients, “richly sampled”
- Various modelling
- Good correlation full AUC and trough (r=0.97)

Neely, AAC, 2014, 58, 309-316.
**Dosing & Elimination**

- **Correlation Trough – AUC$_{24}$**

  Ryback Am J health Syst Pharm 2009, 66, 82-98

  Good correlation

  \[ r^2 = 0.44; \ P < 0.01 \]

  \[ r^2 = 0.97, \ p = 0.016 \]

  Trough 16.6 - 20.9 µg/mL; 24h AUC/MIC 455 - 541

  Jeffres, Chest, 2006;130: 947-55

  Vandecasteele, CID, 2011;53:124-9
Poor tissue penetration

- **Brain**: 10% (0-48%)
  - Lutsar, CID, 1998, 27, 1117-1129

- **Lung fluid**: < 10% serum
  - Georges, EJCMID, 1997, 16, 385-388

- **Bone and skin**: ~ 20%
  - Fat < 10%
  - Kitzes-Cohen, 2000, Ther Drug Monitor, 22, 661-667

- **Intracellular**: “no activity”
  - Valou, 2015, 59, 2029-2036

- **Diabetic foot**: “under target”
  - Hamada, 2015, JAC, Eprint

**CAVE**: methodological issues with interpretation tissue concentrations

- Mouton, 2008, JAC, 61, 235-237
<table>
<thead>
<tr>
<th></th>
<th>Normal renal function</th>
<th>Renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral absorption</td>
<td>Very low</td>
<td>9.1 (CrCl &gt; 60)</td>
</tr>
<tr>
<td>α-Distribution phase</td>
<td>30–60 min</td>
<td>32.3 (60 &gt; CrCl &gt; 10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>146.7 (10 &gt; CrCl)</td>
</tr>
<tr>
<td>Half-life (hours)</td>
<td>6–12</td>
<td></td>
</tr>
<tr>
<td>Renal clearance</td>
<td>3.66+(0.689 × CrCl) ml/min</td>
<td>Unknown</td>
</tr>
<tr>
<td>Extrarenal clearance (%)</td>
<td>5–8.5</td>
<td></td>
</tr>
<tr>
<td>Dialysance (%)</td>
<td>89.6–93.4</td>
<td></td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>50–55</td>
<td>20</td>
</tr>
<tr>
<td>Tissue penetration</td>
<td>Variable, but generally low</td>
<td></td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>0.4–1 l/kg</td>
<td>0.72–0.9 l/kg</td>
</tr>
<tr>
<td>PK/PD parameter</td>
<td>AUC/MIC</td>
<td></td>
</tr>
<tr>
<td>Drug monitoring</td>
<td>Trough levels</td>
<td>(target 15–20 μg/ml)</td>
</tr>
<tr>
<td></td>
<td>Post-antibiotic effect</td>
<td>0.2–2 h (in S. aureus)</td>
</tr>
</tbody>
</table>

Vandecasteele, JAC, 2013, 68, 743-748
Evidence based

1. IV administration, complex PK
2. Variable, often poor, tissue penetration
3. Red men: 15 mg/min IV
4. **Loading dose:**
   → More rapidly target attainment
   → Body weight based (30-35 mg/kg ?)
5. **Maintenance dose:**
   → Body weight and Cl_{Cr} based
6. **Drug monitoring:** Trough ~ AUC_{24}
Unresolved issues

1. Total or free vancomycin concentrations?
2. Best method to measure vancomycin concentrations
3. Extend of non-renal elimination?
4. Loading dose? How much?
5. Exact influence of renal failure on dosing?
6. How to estimate renal function?
7. Correlation AUC$_{24}$ and through levels
8. What maintenance dose?
9. …
2. Pharmacodynamics of vancomycin (PK)

- Dosing & Elimination
  - Serum concentrations
    - Varying over time
    - Concentrations in non-target tissues
      - MINIMUM
      - MAXIMUM
    - Concentrations at the site of the infection
      - Therapeutic effect
      - Toxic effect
Therapeutic effect

S. aureus

Osmotic cytolysis may take up to 32 hours

Couvalin, 2006, CID, 42, S25-S34
Therapeutic effect

**S. aureus**

- Killing curve = for 2, 4, 8, 16 and 64 x MIC (Inoculum $10^5$ S. aureus)
- Higher concentrations $\rightarrow$ long PAE
- $\rightarrow$ Time dependent killing

Foreign bodies: no killing

- MBC > 256 times MIC

Lowdin AAC, 1998, 42, 2739-2744

Chuard, JID, 1991, 163, 1369-1373
• **Nafcillin** and **daptomycin**: bactericidal activity after 4 hours
• **Vancomycin**: bactericidal activity after 48 hours

The inoculum effect of vancomycin:

5x10^5 \downarrow 3 \text{ log/48 hour}

5x10^9 \downarrow < 1 \text{ log/48 hour}

The inoculum effect of vancomycin:

- Neutropenic mouse
- 2 different MRSA strains
- High (triangle) and low (circle) inoculum injected in opposite tight

Lee, AAC, 2013, 57, 1434-1441.
Therapeutic effect

hVISA & creep in MIC

Liu, AAC, 2003, 47:3040-5.

Edwards, J Clin Microbiol 2012; 50:318-325
Inherent toxicity: nephrotoxicity

- 12 – 43 %; dialysis needed in 5 – 30 % of the severely ill
  Vandecasteele, 2010, KI, 77, 760-64
  Van Hal, AAC, 2013, 57, 734-744.

- Incremental with dose (amount and duration)
  Lodise, 2008, AAC, 52, 1330-1336
  Lodise, 2009, CID, 49, 507-514
  Carreno, 2013, Infect Dis Therapeut, 2, 201-208
  Hanrahan, 2014, Crit Care Med, 42, 2527-2536
  Van Hal, AAC, 2013, 57, 734-744.
Inherent toxicity: nephrotoxicity

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>High troughs ≥15mg/L</th>
<th>Low trough &lt;15mg/L</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosso et al. (21)</td>
<td>42</td>
<td>142</td>
<td>4.30 [2.19, 8.43]</td>
</tr>
<tr>
<td>Cano et al. (22)</td>
<td>22</td>
<td>89</td>
<td>4.32 [1.74, 10.69]</td>
</tr>
<tr>
<td>Chung et al. (23)</td>
<td>12</td>
<td>25</td>
<td>1.85 [0.69, 4.96]</td>
</tr>
<tr>
<td>Hermens et al. (30)</td>
<td>5</td>
<td>16</td>
<td>3.98 [0.91, 17.46]</td>
</tr>
<tr>
<td>Hidayat et al. (13)</td>
<td>11</td>
<td>63</td>
<td>14.24 [0.81, 249.87]</td>
</tr>
<tr>
<td>Jeffres et al. (15)</td>
<td>27</td>
<td>49</td>
<td>3.02 [1.28, 7.11]</td>
</tr>
<tr>
<td>Kralovicova et al. (31)</td>
<td>21</td>
<td>60</td>
<td>2.02 [1.04, 3.96]</td>
</tr>
<tr>
<td>Kullar et al. (32)</td>
<td>8</td>
<td>116</td>
<td>6.15 [0.75, 50.13]</td>
</tr>
<tr>
<td>Kullar et al. (8)</td>
<td>27</td>
<td>139</td>
<td>1.24 [0.67, 2.28]</td>
</tr>
<tr>
<td>Lodise et al. (36)</td>
<td>7</td>
<td>27</td>
<td>3.13 [1.12, 8.69]</td>
</tr>
<tr>
<td>McKamy et al. (38)</td>
<td>16</td>
<td>57</td>
<td>4.98 [1.98, 12.52]</td>
</tr>
<tr>
<td>Minejima et al. (39)</td>
<td>17</td>
<td>72</td>
<td>1.61 [0.80, 3.21]</td>
</tr>
<tr>
<td>Prabaker et al. (43)</td>
<td>7</td>
<td>54</td>
<td>1.68 [0.68, 4.11]</td>
</tr>
<tr>
<td>Wunderink et al. (50)</td>
<td>26</td>
<td>118</td>
<td>2.25 [1.22, 4.13]</td>
</tr>
<tr>
<td>Zimmermann et al. (51)</td>
<td>8</td>
<td>12</td>
<td>126.56 [6.19, 2585.90]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1039 1718 100.0% 2.67 [1.95, 3.65]

Total events 256 201

Heterogeneity: Tau² = 0.14; Chi² = 23.89, df = 14 (P = 0.05); I² = 41%

Test for overall effect: Z = 6.13 (P < 0.00001)

Van Hal, AAC, 2013, 57, 734-744.
Inherent toxicity: nephrotoxicity

- Risk is higher for IA than for CI → peak concentration ??
  - Hanrahan, 2014, Crit Care Med, 42, 2527-2536

- Increased with co-administration of other nephrotoxic drugs, e.g. aminoglycosides, loop diuretics, vasopression, ...
  - Ryback, 1990, JAC, 55,679-687
  - Hanrahan, 2014, Crit Care Med, 42, 2527-2536
Inherent toxicity: nephrotoxicity

Retrospective analysis, 1430 treatment courses, ICU, Rifle criteria

- OR 1.112 [1.038-1.139] for medium vanco concentration p<0.001
- OR 1.041 [1.028-1.054] for duration (days) p<0.001

**TABLE 5. Precision of Predicting Nephrotoxicity and Incremental Risk Increase of Different Threshold Values for Highest Measured Vancomycin Serum Concentrations**

<table>
<thead>
<tr>
<th>Threshold Level (mg/L)</th>
<th>Nephrotoxicity (%)</th>
<th>Relative Risk Increase*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Youden Index</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>21.7%</td>
<td>1</td>
<td>0.043</td>
<td>0.043</td>
<td>0.217</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>23.2%</td>
<td>1.069</td>
<td>0.936</td>
<td>0.178</td>
<td>0.115</td>
<td>0.232</td>
<td>0.914</td>
</tr>
<tr>
<td>20</td>
<td>26.2%</td>
<td>1.207</td>
<td>0.84</td>
<td>0.372</td>
<td>0.212</td>
<td>0.262</td>
<td>0.898</td>
</tr>
<tr>
<td>25</td>
<td>33.1%</td>
<td>1.525</td>
<td>0.747</td>
<td>0.600</td>
<td>0.346</td>
<td>0.331</td>
<td>0.899</td>
</tr>
<tr>
<td>30</td>
<td>41.5%</td>
<td>1.912</td>
<td>0.603</td>
<td>0.774</td>
<td>0.377</td>
<td>0.415</td>
<td>0.880</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>47.9%</td>
<td>2.207</td>
<td>0.303</td>
<td>0.912</td>
<td>0.216</td>
<td>0.478</td>
<td>0.831</td>
</tr>
</tbody>
</table>

*Relative to first threshold level (10 mg/L).

Hanrahan, 2014, Crit Care Med, 42, 2527-2536
Inherent toxicity: ototoxicity

high frequency hearing loss - in up to 12 % of the patients when used longer time.


Ideosyncratic toxicity

neutropenia, hypersensitivity reactions, ...

Matzke, 1986, Clinical Pharmacokinetics, 11 257-280
Evidence based

1. **Bactericidal antibiotic** with
   i. Slow mode of action
   ii. Time dependent killing activity
   iii. Important inoculum and stationary phase effect

2. **Major problem of nephrotoxicity**
   i. Incremental with dose (amount and duration)
   ii. Most pronounced in case of other nephrotoxic factors (medication, hypoperfusion)
   iii. Less in CI than in IA: peak effect?
Unresolved issues

2. Exact dose/effect correlation?
3. Exact dose/renal toxicity correlation?
4. Reversibility renal toxicity?
5. Effect renal toxicity on outcome?
6. ...
Pharmacodynamics of vancomycin (PD)

- Toxic effect
- Therapeutic effect
- Minimum
- Maximum
3. PK/PD of vancomycin
$\text{AUC}_{24}/\text{MIC}$ as vancomycin PK/PD index?
Experimental ground of AUC/MIC model:

Experimental mouse model
Never published; 1987 ICAAC

Ryder, CID, 2006; 42: S35–9
1) 108 ptنت with pneumonia calculated $AUC_{24}$ in 78 (!) ptنت

$AUC_{24}/MIC$:
- 345 clinical cure
- 850 microbiological cure

Moise-Broder, Clin Pharmacokinet, 2004;43: 925-942
Clinical grounds of AUC/MIC model:

2) 102 ptm HA pneumonia, calculated AUC_{24}
*No correlation* through or AUC with outcome

Jeffres' 2006 Chest, 130, 947-955

3) 50 complicated MRSA bacteremia retrospective, calculated AUC_{24}
*correlation* outcome (4x higher mortality) with AUC_{24}/MIC of < or > 211


4) Retrospective cohort of 182 SAB, calculated AUC_{24}/MIC
No correlation with 30-day mortality for AUC_{24}/MIC ≥ 400, but
*correlation* when cut-off of > 375 is used (p=0.043)

Holmes, AAC, 2013, 57, 1654-1663
Clinical grounds of AUC/MIC model:

5) 139 pttn MRSA endocarditis, 76.3 % right-side failure = 30 d mortality or > 7 d bacteremia

calculated AUC$_{24}$, retrospective cohort

Correlation with failure 69.8 versus 54.7 % for AUC < or > than 600

p = 0.073

Casapao, 2015, AAC, Eprint.
Which AUC/MIC is feasible?

<table>
<thead>
<tr>
<th>MIC value</th>
<th>AUC/MIC ratio ≥400 (%)</th>
<th>Nephrotoxic event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5mg/L</td>
<td>1.0mg/L</td>
</tr>
<tr>
<td>500 mg IV Q12H</td>
<td>57</td>
<td>15</td>
</tr>
<tr>
<td>1000 mg IV Q12H</td>
<td>90</td>
<td>57</td>
</tr>
<tr>
<td>1500 mg IV Q12H</td>
<td>97</td>
<td>79</td>
</tr>
<tr>
<td>2000 mg IV Q12H</td>
<td>98</td>
<td>90</td>
</tr>
</tbody>
</table>

Extensive modelling
Data from 37 patients

**Target levels:**
No hard outcome data!!

Efficacy: the higher, the better
Toxicity: the lower, the better ...

Data derived from AUC/MIC modelling:
- **Intermittent administration:** 15-20 μg/ml
- **Continuous infusion:** 20-25 μg/ml
CI or IA? → time dependent AB
   → No hard outcome data!!

- Less renal toxicity for CI
- More rapid target attainment (3 versus 4 days – p=0.022)
- Less sub-therapeutic levels (41 versus 11% - p<0.001)
  (125 ptn, prospective, surgical ICU)

Tafelski, J of Infection and Public Health, 2015, Eprint
Hanrahan, 2014, Crit Care Med, 42, 2527-2536
Evidence based

1. There is a correlation between effect and AUC/MIC: the higher, the more effect.
2. Continuous infusion seems to be safer and results in more rapidly target attainment.
Unresolved issues

1. What PK/PD parameter best predicts effect?
2. How does this PK/PD parameter correlate with outcome?
3. Does TDM predict this PK/PD parameter?
4. Do through levels predict effect?
5. What are the best target through levels?
6. Should vancomycin be administered as CI or IA?
7. ...
CONCLUSION

Can optimization of vancomycin dosing improve outcome (mortality and morbidity)?