Pharmacokinetics and pharmacodynamics of gentamicin and vancomycin

Alison H Thomson
University of Strathclyde, NHS Greater Glasgow and Clyde
Structure of presentation

• **Gentamicin**
  – Concentration-effect relationships
  – Pharmacokinetics
  – Dosage regimen design

**Questions**

• **Vancomycin**
  – Concentration-effect relationships
  – Pharmacokinetics
  – Dosage regimen design

**Questions**
Gentamicin efficacy

- “Cure” associated with peaks >4-5 mgL$^{-1}$ (n=68)
  *Noone et al, BMJ, 1974*

- Mortality from gm-ve septicaemia reduced if peak >5 mgL$^{-1}$
  *Moore et al, Ann Int Med 1984*

- Max peak : MIC ratio determined clinical response (n = 263)
  *Moore et al, J Inf Dis 1987*
Aminoglycoside nephrotoxicity

Bertino et al, 1993 (n = 1489)
- Risk factors: $C_{\text{min}}^{\text{ss}}$, other antibiotics, male, elderly, low albumin, prolonged duration, leukaemia

Murry et al, 1999 (n = 200 ODA and 100 TDA)
- <40 ml/min$^{-1}$ excluded
- Nephrotoxicity: 7.5% vs 14.7% (NS)
- Risk factors: cumulative AUC, other nephrotoxic drugs
Randomised comparison of nephrotoxicity and ototoxicity (therapy >72 h)

39 patients twice daily, 35 once daily (placebo 12 h)

Nephrotoxicity: ↑creatinine 44 μmol/L or 50%
  - 6 (15.4%) twice daily after 8.8 (3.4) days
  - 0 once daily

Risk factors: Daily AUC, twice daily dosing, concomitant vancomycin
Prospective Evaluation of the Effect of an Aminoglycoside Dosing Regimen on Rates of Observed Nephrotoxicity and Ototoxicity

MICHAEL J. RYBAK,1,2* BETTY J. ABATE,1† S. LENA KANG,1‡ MICHAEL J. RUFFING,1 STEPHEN A. LERNER,2 AND GEORGE L. DRUSANO3

Probability curve “twice daily”

Probability curve “once daily”

Antimicrobial Agents and Chemotherapy, July 1999, p. 1549–1555
Aminoglycoside ototoxicity

- Excessive production of oxidative free radicals → apoptosis of hair cells

- Idiosyncratic (hearing)
  - mutation in the mitochondrial 12S ribosomal RNA
  - 3 other mutations identified in the same gene
  - 30% of patients with ototoxicity carry mutation.

- In future – prevent
  - free radical scavengers?
  - genetic monitoring?
Incidence of Amikacin Ototoxicity:
A Sigmoid Function of Total Drug Exposure Independent of Plasma Levels

A. R. Brubier, PhD, S. Desjardins, PhD, E. Ormsby, MSc, A. Bayne, K. Carrier, M. J. Caughey, R. Henri, M. Hodgen, BSc, J. Salley, B. Eng, and A. St. Pierre

Guinea pig data
• 10.9% gentamicin, 7.4% amikacin, 3.5% tobramycin
• **Clinic data**: duration of Rx 17 – 41 days (median 28)
• **Time-dependent**, not dose, conc or AUC (?)
• **Sudden onset**
  – usually irreversible
  – may appear after antibiotic stopped
  – difficult to test in critically ill
  – stop or change antibiotic if dizziness occurs
Aminoglycoside pharmacokinetics

• Clearance depends on renal function
  – Cockcroft Gault Equation
    IBW vs TBW vs Dosing weight?
    Poor at low GFR
  – eGFR (readily available)
    Normalised for 1.73 m²
    Maximum 60 ml/min/1.73m²

• Volume of distribution depends on weight
  – Ideal body weight?
  – Total body weight?
  – Dosing weight?
Influence of body weight on aminoglycoside pharmacokinetics  

<table>
<thead>
<tr>
<th></th>
<th>Normal (n = 12)</th>
<th>Morbidly Obese (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>73 (7.5)</td>
<td>138 (15)</td>
</tr>
<tr>
<td>V (L/kg TBW)</td>
<td>0.25 (0.04)</td>
<td>0.17 (0.04)</td>
</tr>
<tr>
<td>V (L/kg IBW)</td>
<td>0.26 (0.05)</td>
<td>0.41 (0.1)</td>
</tr>
<tr>
<td>Cl (ml/min/kg TBW)</td>
<td>1.02 (0.42)</td>
<td>1.31 (0.24)</td>
</tr>
</tbody>
</table>

\( V_{\text{gentamicin}} = 0.26 \times (\text{IBW} + 0.45 \times (\text{TBW} - \text{IBW})) \)
“Dosing weight” correction factor - problems

• **Interindivudual variability**
  – Correction factor range 0.19 – 0.98
  – Does not account for body composition, muscle vs fat

• Assumes linear relationship with obesity
Dosing in Obesity: A Simple Solution to a Big Problem

PY Han¹, SB Duffull¹,², CMJ Kirkpatrick¹ and B Green¹

For males:

\[\text{LBW}_{2005} \ (\text{kg}) = \frac{9270 \times \text{WT (kg)}}{6680 + 216 \times \text{BMI (kg m}^{-2}\text{)}}\]

For females:

\[\text{LBW}_{2005} \ (\text{kg}) = \frac{9270 \times \text{WT (kg)}}{8780 + 244 \times \text{BMI (kg m}^{-2}\text{)}}\]
“Dosing weight” correction factor - problems

• **Interindividual variability**
  – Correction factor range 0.19 – 0.98
  – Does not account for body composition, muscle vs fat

• **Assumes linear relationship with obesity**

• **Does not distinguish between effects on CL and V**
Concentration profiles: IBW 80 kg TBW 140 kg
“Dosing weight” correction factor

- **Interindivdual variability**
  - Correction factor range 0.19 – 0.98
  - Does not account for body composition, muscle vs fat, critical illness burns, etc.

- Assumes linear relationship with obesity

- Does not distinguish between effects on CL and V

...but is a reasonable starting point
Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily

C. M. J. Kirkpatrick, S. B. Duffull & E. J. Begg
Department of Clinical Pharmacology, Christchurch Hospital, PO Box 4710, Christchurch, New Zealand

• Clearance vs “CLCr adjusted to a minimum of 60 μmol/L ($r^2 = 0.80$)

• CL vs CLCr, unadjusted ($r^2 = 0.57$)
Population pharmacokinetics of gentamicin in patients with cancer


Measured creatinine

R-sq = 43.2%

<60 set to 60 micromol/L

R-sq = 60%
Development of new GGC guidelines for gentamicin dosing and monitoring
Position in July 2008

• Mixture of dosage guidelines and monitoring approaches
  – North Glasgow: “new guidelines – 24 hourly table”
  – South Glasgow: “old guidelines – 12/24 hourly table”
  – Inverclyde: 5 mg/kg 24, 36, 48 hourly
  – RAH: mixture

• Single system: need for consistency across Greater Glasgow and Clyde

• Need to balance practicality with demands of
  – Microbiology: increase dose
  – Renal physicians: reduce dose
North Glasgow Service Evaluation

*Kimberley Neil, Pharmacy WIG*

- TDM forms (clinical and demographic data, doses, times, concentrations)

- Forms reviewed
Variance from guideline dose amount n = 226)

- 31% higher
- 22% lower

Patient ID number

Difference in mg

31%

NHS
Greater Glasgow and Clyde

University of Strathclyde
North Glasgow Service Evaluation

Kimberley Neil, Pharmacy WIG

• TDM forms (clinical and demographic data, doses, times, concentrations)

• Forms reviewed

• PK analysis with “OPT” to get individual estimates of CL and V

• Simulations of predicted concentrations with a range of dosage options
  – peak, trough and AUC compared
<table>
<thead>
<tr>
<th>Predicted trough</th>
<th>North Guidelines n = 204</th>
<th>Initial Dose n = 204</th>
<th>South Guidelines n = 204</th>
<th>5 mg/kg IBW n = 204</th>
<th>5 mg/kg TBW n = 204</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) mg/L</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.5 mg/L</td>
<td>0.8 (1.3)</td>
<td>0.8 (1.2)</td>
<td>1.0 (1.2)</td>
<td>0.5 (0.8)*</td>
<td>0.7 (1.2)</td>
</tr>
<tr>
<td></td>
<td>61.3%</td>
<td>58.3%</td>
<td>33.8%</td>
<td>72.5%</td>
<td>68.1%</td>
</tr>
<tr>
<td>&lt;1 mg/L</td>
<td>74.0%</td>
<td>73.5%</td>
<td>63.7%</td>
<td>85.3%</td>
<td>80.9%</td>
</tr>
<tr>
<td>1-2 mg/L</td>
<td>12.7%</td>
<td>11.8%</td>
<td>22.5%</td>
<td>9.3%</td>
<td>10.8%</td>
</tr>
<tr>
<td>&gt;2 mg/L</td>
<td>13.2%</td>
<td>14.7%</td>
<td>13.7%</td>
<td>5.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Predicted 1 h post infusion concentration</td>
<td>North Guidelines n = 204</td>
<td>Initial Dose n = 204</td>
<td>South Guidelines n = 204</td>
<td>5 mg/kg IBW n = 204</td>
<td>5 mg/kg TBW n = 204</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------------</td>
<td>----------------------</td>
<td>---------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Mean (SD) mg/L</td>
<td>11.3 (3.6)</td>
<td>11.7 (2.3)</td>
<td>6.6 (1.3)*</td>
<td>12.3 (2.3)</td>
<td>14.1 (3.2)**</td>
</tr>
<tr>
<td>&lt;8 mg/L</td>
<td>4.4%</td>
<td>17.2%</td>
<td>86.8%</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
<tr>
<td>&gt;8 mg/L</td>
<td>95.6%</td>
<td>83.8%</td>
<td>13.2%</td>
<td>99.0%</td>
<td>99.5%</td>
</tr>
<tr>
<td>&gt;10 mg/L</td>
<td>80.4%</td>
<td>63.7%</td>
<td>2.2%</td>
<td>88.7%</td>
<td>97.5%</td>
</tr>
</tbody>
</table>
Gentamicin – report to ADTC

Results

• 5 mg/kg best overall
  – requires 36 hourly dosing
  – separate guidelines if CrCL <30 ml/min
  – needs extensive pharmacy support

ADTC Antimicrobial Utilisation Subcommittee

• Requested doses up to 5 mg/kg 24 or 48 hourly
<table>
<thead>
<tr>
<th>Creat Cl (ml/min)</th>
<th>40 - 49 kg</th>
<th>50 - 59 kg</th>
<th>60 - 69 kg</th>
<th>70 - 80 kg</th>
<th>&gt; 80 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mg/kg (max 180 mg) then take a sample after 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21 - 30</td>
<td>180 mg 48 h</td>
<td>200 mg 48 h</td>
<td>240 mg 48 h</td>
<td>240 mg 48 h</td>
<td>260 mg 48 h</td>
</tr>
<tr>
<td>31 - 40</td>
<td>200 mg 48 h</td>
<td>240 mg 48 h</td>
<td>280 mg 48 h</td>
<td>300 mg 48 h</td>
<td>320 mg 48 h</td>
</tr>
<tr>
<td>41 - 50</td>
<td>240 mg 48 h</td>
<td>280 mg 48 h</td>
<td>320 mg 48 h</td>
<td>360 mg 48 h</td>
<td>400 mg 48 h</td>
</tr>
<tr>
<td>51 - 60</td>
<td>200 mg 24 h</td>
<td>240 mg 24 h</td>
<td>280 mg 24 h</td>
<td>300 mg 24 h</td>
<td>320 mg 24 h</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>240 mg 24 h</td>
<td>280 mg 24 h</td>
<td>320 mg 24 h</td>
<td>360 mg 24 h</td>
<td>400 mg 24 h</td>
</tr>
</tbody>
</table>
New dosage guidelines - predictions

<table>
<thead>
<tr>
<th>Predicted results</th>
<th>Peak (mg/L)</th>
<th>Trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td><strong>11.5 (2.1)</strong></td>
<td><strong>0.4 (0.6)</strong></td>
</tr>
<tr>
<td>Range</td>
<td>&lt;8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>%</td>
<td>3.9</td>
<td>96.1</td>
</tr>
</tbody>
</table>
Profiles for 0.25 and 0.31 L/kg at 50 ml/min and 20 ml/min

Concentration (mg/L) vs. Time (hours)

- 50/24 h 0.25 L/kg
- 20/48 h 0.25 L/kg
- 50/24 h 0.31 L/kg
- 20/48 h 0.31 L/kg
- 50/24 h 0.28 L/g 1 h inf
- 20/48 h 0.28 l/kg 1 h inf
**Time after the start of the infusion**

<table>
<thead>
<tr>
<th>Concentration (mg/L)</th>
<th>0.0</th>
<th>1.0</th>
<th>2.0</th>
<th>3.0</th>
<th>4.0</th>
<th>5.0</th>
<th>6.0</th>
<th>7.0</th>
<th>8.0</th>
<th>9.0</th>
<th>10.0</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target sampling time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If the measured concentration is above this line, withhold until the concentration is <1 mg/L and seek advice.

Give the same dose every 48 hours.

If the measured concentration is below this line, give the same dose every 24 hours.
Comments

• The guidelines will not be appropriate for all patients
• Patients close to the 24 / 48 hour cut-offs are most likely to need a change
• Nomogram is only as good as the quality of the data  
  – If the result looks strange – get another sample
• If the patient is obese or you don’t know what is going on, get 2 samples and work out the actual CL and V, or at least t1/2
• If renal function is unstable, check every day…
Questions on gentamicin?
Vancomycin efficacy and toxicity

Therapeutic monitoring of vancomycin in adult patients: a consensus review
Rybak et al, Am J Health-Syst Pharm 66: 1 Jan 2009
Comments

• Few prospective or randomised trials
• Most data observational

• **Pharmacokinetics**
  – mainly renal clearance but highly variable
  – multiexponential decline (2, 3 cpt models)
  – 50 – 55% protein bound
  – distribution to tissues varies, affected by inflammation and disease
Concentration-effect relationships

- 108 patients, MRSA
- Better outcome if $\text{ssAUC}_{24} / \text{MIC} \geq 400 \text{ mg.h/L}$
- No relationship with time $> \text{MIC}$

**Jeffres et al**, Chest 130: 947, 2006
- 102 patients, retrospective study
- No difference in trough (14 mg/L) or AUC (350 mg.h/L) between survivors and non-survivors (no MIC data)
Nephrotoxicity and ototoxicity

• Early reports: impure product

• Nephrotoxicity
  – May potentiate aminoglycoside nephrotoxicity
  – trough >15 or >20 mg/L
  – Css average >28 mg/L
  – AUC >952 mg.h/L
  – Intermittent vs continuous infusion?

• Ototoxicity
  – Little evidence if monotherapy
Dosage guidelines (Consensus)

• Loading dose
  – 20 – 30 mg/kg TBW

• Maintenance dose
  – No guidelines available for troughs of 15 – 20 mg/L or AUC/MIC > 400 mg.h/L
  – 3 – 4 grams daily?
  – 15 – 20 mg/kg TBW every 8 – 12 hours?
Concentration-effect relationships: troughs

- 5 – 10 mg/L too low to achieve target AUC/MIC
  - Therapeutic failure, reduced sensitivity?

- Continuous infusion: 15 – 25 mg/L
  - Easier to administer and monitor in critical care
  - No evidence of better outcome

- Consensus:
  - Maintain trough >10 mg/L, aim for 15 – 20 mg/L
Development of new vancomycin dosage guidelines
Methods

- Routine TDM data collected from 399 patients (Bristol and Glasgow)

- Population pharmacokinetic analysis examined
  - age, TBW, LBW, LBW$_2$, BSA, serum creatinine
  - Creatinine clearance
    Cockcroft-Gault (TBW, LBW, IBW)
    Jelliffe and Jelliffe
    Salazar Corcoran
    MDRD (LBW)
Results – biexponential decline

\[ Cl = 2.99 \text{ L/h} +/- 15\% \text{ for } 10 \text{ ml/min} \]

\[ \text{from 66 ml/min} \quad 27\% \]

\[ V1 = 0.68 \text{ L/kg TBW} \]

\[ 15\% \]

\[ V2 = 0.73 \text{ L/kg TBW} \]

\[ 130\% \]
Methods

Current dosage guidelines modified

Applied to 110 simulated patients
weight 40 – 120 kg, CrCL 15 – 125 ml/min

Troughs predicted using PopPk model

Predictions compared with 10 – 15 mg/L

New dosage guidelines finalised
CONTINUOUS INFUSION

1. **Loading Dose**
   - Weight <40 kg: 500 mg over 1 hour
   - Weight 40-70 kg: 1000 mg over 2 hours
   - Weight >70 kg: 1500 mg over 3 hours

2. **Maintenance Infusion**
   Start immediately after the loading dose and adjust according to concentration, first measured after 12 – 24 hours of infusion and checked every 24 – 48 hours thereafter.

<table>
<thead>
<tr>
<th>Creat Cl (ml/min)</th>
<th>Daily Dose</th>
<th>Dose for infusion in 250 ml saline over 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>500 mg</td>
<td>250 mg</td>
</tr>
<tr>
<td>20-34</td>
<td>750 mg</td>
<td>375 mg</td>
</tr>
<tr>
<td>35-59</td>
<td>1000 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>60-79</td>
<td>1500 mg</td>
<td>750 mg</td>
</tr>
<tr>
<td>80-99</td>
<td>2000 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>&gt;100</td>
<td>2500 mg</td>
<td>1250 mg</td>
</tr>
</tbody>
</table>
### B. PULsed INFUSION

1. **Loading Dose**

<table>
<thead>
<tr>
<th>Creat Cl</th>
<th>≤ 60 kg</th>
<th>&gt; 60 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 75 ml/min</td>
<td>1000 mg over 2 h, 12 - 48 hours later start <strong>maintenance dose</strong></td>
<td>1000 mg over 2 h, 12 hours later give 1000 mg over 2 h, 12 - 48 hours later start <strong>maintenance dose</strong></td>
</tr>
<tr>
<td>&gt;75 ml/min</td>
<td>Loading dose not required - start maintenance dose</td>
<td></td>
</tr>
</tbody>
</table>
2. Maintenance Dose

<table>
<thead>
<tr>
<th>Creat Cl (ml/min)</th>
<th>Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>500 mg over 1 h</td>
<td>48 hours</td>
</tr>
<tr>
<td>20 - 30</td>
<td>500 mg over 1 h</td>
<td>24 hours</td>
</tr>
<tr>
<td>31 - 40</td>
<td>750 mg over 1.5 h</td>
<td>24 hours</td>
</tr>
<tr>
<td>41 - 55</td>
<td>500 mg over 1 h</td>
<td>12 hours</td>
</tr>
<tr>
<td>56 - 75</td>
<td>750 mg over 1.5 h</td>
<td>12 hours</td>
</tr>
<tr>
<td>76 - 89</td>
<td>1000 mg over 2 h</td>
<td>12 hours</td>
</tr>
<tr>
<td>90 - 120</td>
<td>1250 mg over 2.5 h</td>
<td>12 hours</td>
</tr>
<tr>
<td>&gt;120</td>
<td>1500 mg over 3 h</td>
<td>12 hours</td>
</tr>
</tbody>
</table>

Target concentration (trough at end of dosage interval) is 10 – 15 mg/L (standard) or 15-20 mg/L (severe or deep seated infections) ...
Evaluation of new guidelines

• Vancomycin concentration data and dosage regimens identified for a 100 new patients (WIG)

• Individual CL and V estimated
  – PopPK model with Bayesian analysis (NONMEM)

• Simulated dosage histories created for each patient
  – current North Glasgow guidelines
  – new guidelines

• Steady state trough concentrations and $\text{AUC}_{24}$ predicted
Vancomycin profiles: current dosage guidelines

Note median around 10 mg/L, low concs over the first 1-2 days
Vancomycin profile: new guidelines
Comparison of old and new guidelines

<table>
<thead>
<tr>
<th></th>
<th>Current guidelines (n = 100)</th>
<th>New guidelines (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Css minimum</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Css maximum</td>
<td>41</td>
<td>34</td>
</tr>
<tr>
<td>Css mean (SD)</td>
<td>18.2 (4.3)</td>
<td>21.1 (3.7)</td>
</tr>
<tr>
<td>AUC mg.h/L</td>
<td>436 (104)</td>
<td>505 (88)</td>
</tr>
</tbody>
</table>
Comparison of old and new guidelines

<table>
<thead>
<tr>
<th>Predicted conc range</th>
<th>Current guidelines (n = 1013)</th>
<th>New guidelines (n = 1360)</th>
<th>99% CI of difference in prop</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg/L</td>
<td>0.61 (61%)</td>
<td>0.25 (25%)</td>
<td>-0.31 to -0.41*</td>
</tr>
<tr>
<td>10 – 15 mg/L</td>
<td>0.32 (32%)</td>
<td>0.44 (44%)</td>
<td>0.07 to 0.17*</td>
</tr>
<tr>
<td>15 – 20 mg/L</td>
<td>0.06 (6%)</td>
<td>0.25 (25%)</td>
<td>0.16 to 0.23*</td>
</tr>
<tr>
<td>&gt; 20 mg/L</td>
<td>0.01 (1%)</td>
<td>0.06 (6%)</td>
<td>0.03 to 0.06*</td>
</tr>
</tbody>
</table>
Summary Comments

• **Guidelines are just a starting point** –
  – Wide interpatient variability
  – Changing clinical situations
  – Close monitoring of creatinine (and concentrations) required

• **Gentamicin guidelines**
  – Audit ongoing but further evaluation required

• **Vancomycin guidelines**
  – Revision of loading doses ongoing
  – Audit required