Update on Therapeutic Drug Monitoring - Aminoglycosides

Antimicrobial Stewardship Forum
Cardiff Nov. 2nd 2015

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North Bristol NHS Trust
What are common reasons for clinicians to request antibiotic assays?

- Patient event consistent with reported adverse event profile of drug
- Concern about penetration to deep site
- Concern about treating marginal susceptibility
- Issues of compliance/absorption
- Patient factors that may affect drug handling
  - Renal/Hepatic clearance & support, obesity, ECMO, extremes of age, severe sepsis, burns, missing limbs
- To prevent the need to change or suspend therapy

“Can TDM address some or all of these?”
Where is TDM justified?

• Where exposure predicts toxicity
  – Aminoglycosides, vancomycin, colistin, ethambutol, cycloserine, flucytosine, voriconazole

• Where exposure predicts clinical cure or resistance emergence
  – Teicoplanin, vancomycin, posaconazole, itraconazole, aminoglycosides

• Where dose poorly predicts exposure
  – Physiological abnormalities, extra-corporeal support, oral agents
Clinician’s Perspective of TDM

National and Local Policy

- Maintain pre dose below 1mg/L
- If above 1mg/L increase dosing interval

“Targets are clear and action to take when these are not achieved is defined – very much a black or white approach to TDM”

Toxic Concentration at pre dose
Sub-therapeutic Concentration (E.coli)
“TDM objectives may vary depending on individual perspective and personal interpretation of published data – more of a rainbow approach with no single target”
Drug Accumulation To Steady State

Risk of failure

Risk of toxicity
Physiological Impact of Sepsis on Antimicrobial Drug Handling

Sepsis

Increased Cardiac Output
- Cl ↑
- Reduced Levels (50%)

Leaky Capillaries &/or Protein Binding Changes
- Vd ↑

Normal Organ Function
- Cl & Vd ≈
- Normal Levels (40%)

End Organ Dysfunction
- Cl ↓
- Raised Levels (10%)

How are TDM results used?

“Results without interpretation criteria are of low value and potentially misleading”

Interpretation may be based on:

– Targets related to toxicity or outcome data
– Guideline ranges based on expected pharmacokinetics
– Broad objectives derived from PKPD considerations, clinical practice and gut feeling

“Should there be general guidelines or individualised interpretation?”
Aminoglycoside Dosing and Monitoring
Aminoglycosides Available In The UK

Gentamicin

Tobramycin

Amikacin

Streptomycin

Neomycin
Vancomycin – NOT AN AMINOGLYCOSIDE!
Dosing of Aminoglycosides

• Which patient weight measure should be used?
  – Patient more than 20% above or below IBW
  – Adjusted Body Weight = IBW + 0.4(TBW-IBW) (>20% above IBW)
  – But, remember cardiac output changes

• Which measure of renal function should be used?
  – eGFR poorly predicts gentamicin clearance, Cockcroft Gault or BSA adjusted measures are better

• Calculators or paper based?
Renal Function Measures for Gentamicin Dosing  
(Correlation (Pearson’s r) with gentamicin clearance)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal Patients (n=221)</th>
<th>Obese Patients (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cockcroft Gault (TBW)</td>
<td>0.60</td>
<td>0.54</td>
</tr>
<tr>
<td>Cockcroft Gault (IBW)</td>
<td>0.55</td>
<td>0.61</td>
</tr>
<tr>
<td>Cockcroft Gault (ABW)</td>
<td>0.60</td>
<td>0.59</td>
</tr>
<tr>
<td>MDRD (eGFR)</td>
<td>0.28</td>
<td>0.40</td>
</tr>
<tr>
<td>MDRD (Actual BSA)</td>
<td>0.50</td>
<td>0.52</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>0.48</td>
<td>0.56</td>
</tr>
<tr>
<td>CKD-EPI (Actual BSA)</td>
<td>0.66</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Cockcroft Gault (mL/min) = \((140 - \text{age}) \times \text{weight} \times (1.23 \text{ if male or } 1.04 \text{ if female})\)  
\[
\text{Creat} [\text{micromol/l}]
\]

MDRD (mL/min/1.73 m^2) = \(6 \times (\text{Creat} / 88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})\)

Lim et al. 2015 Int Med J.
Analysis of the accuracy of gentamicin initial doses after introduction of an online calculator

<table>
<thead>
<tr>
<th>Category</th>
<th>Before (%) n=195</th>
<th>After (%) n=215</th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct dose</td>
<td>75 (38.5)</td>
<td>120 (55.8)</td>
<td>2.02</td>
<td>1.36 to 3.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overdose</td>
<td>83 (42.6)</td>
<td>62 (28.8)</td>
<td>0.55</td>
<td>0.36 to 0.82</td>
<td>0.004</td>
</tr>
<tr>
<td>Underdose</td>
<td>37 (19.0)</td>
<td>33 (15.3)</td>
<td>0.77</td>
<td>0.46 to 1.30</td>
<td>0.331</td>
</tr>
</tbody>
</table>

Hamad. 2015 BMJ
Aminoglycoside Nephrotoxicity

• Primarily tubular necrosis through saturable binding to megalin
  – Accumulation to a toxicity threshold

• Overall incidence reported 5% to 30% for EID (Nee OD)
  – 88% patients treated <4d with <1% nephrotoxicity
  – 12% patient treated >4d with 12% nephrotoxicity (onset 8-15d)
  – V. low in neonates increasing to 20-30% in certain patient groups

• Risk increases with: elevated levels, heart failure, duration, concomitant nephrotoxic agents, age and gender

• 25-50% of patients with nephrotoxicity have a poor recovery by 21d

Plajar Ther Drug Mon 2015; Paquette, Nephron 2015.
Aminoglycoside Ototoxicity

• Cochlear and vestibular
  – Accumulation and slow release with T1/2 of 20-40d
  – Some recovery of function seen in 20% of patients
• Genetic disposition due to 12s mitochondrial mutations at normal concentration
  – Maternal transmission and present in 10-20% of case of aminoglycoside-induced ototoxicity (but up to 60%)
  – Incidence of 2% in general population but 15-20% in certain populations (Spanish/Japanese)
  – Cost of screening is about £500 to prevent one case
• Vestibular hard to assess, more common than thought
• Associated with ‘exposure’ rather peak or trough levels

Bilateral Vestibular Damage (Clinic Referrals)

- Gentamicin: 47%
- Cisplatin: 34%
- Meningitis: 11%
- Hereditary: 5%
- Neuritis: 5%
- Idiopathic: 2%

n=552

Amikacin Ototoxicity In Patients with MDR TB

Mean Pre  0.7 vs 0.35 mg/L (hearing loss/no hearing loss)
Mean Post 44.5 vs 49.4 mg/L (hearing loss/no hearing loss)

TDM Objectives

• Toxicity
  – Exposure below threshold for EID?
    • 1 mg/L (Gentamicin/Tobramycin) or 0.5 mg/L
    • 5 mg/L (Amikacin/Streptomycin)
  – Limited risk if short duration (<3d)

• Outcome
  – Maximise Cmax/mic (8-10)
  – Cmax >20mg/L (Gent/Tob) or >40 mg/L (Amik)
  – AUC of 70-100 mg.h/L

Common TDM Control Approaches

- Cmin only
- Cmin and Cmax
- Nomogram
- Two-point method (paper or computer)
- Baysian
Gentamicin Monitoring – Trough Level Only

A. Normal renal function

B. Impaired renal function

C. Augmented renal function

D. Increased volume of distribution
Gentamicin Monitoring – Peak and Trough Level

A. Normal renal function

B. Impaired renal function

C. Augmented renal function

D. Increased volume of distribution

A. Normal renal function:

- Concentration (μg/ml) vs. Time (h)
- Peak concentration >20 mg/L

B. Impaired renal function:

- Concentration (μg/ml) vs. Time (h)
- Peak concentration >20 mg/L

C. Augmented renal function:

- Concentration (μg/ml) vs. Time (h)
- Peak concentration >20 mg/L

D. Increased volume of distribution:

- Concentration (μg/ml) vs. Time (h)
- Peak concentration <20 mg/L
Hartford Nomogram – 7 mg/kg

Known Issues
- Incorrect dose for nomogram
- Incorrect timing of sample draw

NOMOGRAMS

Nicolau AAC 1995
Blood levels of gentamicin for doses of 7-3 mg/kg showing the concentration profiles that could be possibly present when using the 6-hour decision point.
## Gentamicin Nomograms

<table>
<thead>
<tr>
<th>Nomogram</th>
<th>Dose</th>
<th>Cmin &amp; Target Attainment</th>
<th>Cmax and Target Attainment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomson</td>
<td>MDD</td>
<td>1.0 mg/L (90%)</td>
<td>7.9 mg/L (72%)</td>
</tr>
<tr>
<td>Hull-Surubbi</td>
<td>MDD</td>
<td>1.1 mg/L (90%)</td>
<td>5.5 mg/L (59%)</td>
</tr>
<tr>
<td>Rule of Eighths</td>
<td>MDD</td>
<td>1.3 mg/L (83%)</td>
<td>5.0 mg/L (50%)</td>
</tr>
<tr>
<td>Hartford</td>
<td>7 mg/kg EID</td>
<td>0.4 mg/L (95%)</td>
<td>20.4 mg/L (46%)</td>
</tr>
<tr>
<td>Barnes-Jewish</td>
<td>5 mg/kg EID</td>
<td>0.3 mg/L (96%)</td>
<td>15.5 mg/L (6%)</td>
</tr>
<tr>
<td>Sanford</td>
<td>4-5 mg/kg EID</td>
<td>0.4 mg/L (98%)</td>
<td>13.1 mg/L (4%)</td>
</tr>
</tbody>
</table>

**Targets:**  
MDD Cmin <2mg/L and Cmax 5-10mg/L  
EID Cmin <1mg/L and Cmax >20 mg/L

Aminoglycoside Monitoring by 2-point Method

- Cmax at 0, 0.5 or 1h?
- Sampling time points (2h & 10h)
- Clearance overestimated
### Dosing by Levels - Aminoglycosides/ Vancomycin

<table>
<thead>
<tr>
<th>Field</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Drug</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Weight</td>
<td>100 Kg</td>
</tr>
<tr>
<td>Height</td>
<td>180 Centimeters</td>
</tr>
<tr>
<td>Peak level obtained</td>
<td>17.1</td>
</tr>
<tr>
<td>Number hours post dose</td>
<td>0.5</td>
</tr>
<tr>
<td>Trough level obtained</td>
<td>0.3</td>
</tr>
<tr>
<td>Number hours post dose</td>
<td>23.5</td>
</tr>
<tr>
<td>Current dose being given</td>
<td>240</td>
</tr>
<tr>
<td>Current dosing interval</td>
<td>24</td>
</tr>
<tr>
<td>Current infusion time (hrs)</td>
<td>0.5</td>
</tr>
<tr>
<td>Desired peak</td>
<td>25</td>
</tr>
<tr>
<td>Desired trough</td>
<td>0.5</td>
</tr>
</tbody>
</table>

[Calculate Results] [Reset]
<table>
<thead>
<tr>
<th>Calculated Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBW: 75.07 kg</td>
</tr>
<tr>
<td>New rate constant (kel): 0.176 (hr⁻¹)</td>
</tr>
<tr>
<td>New Vd from levels: 13.63 Liters</td>
</tr>
<tr>
<td>Actual Cmax: 17.10 mcg/ml</td>
</tr>
<tr>
<td>Recommended dose: 349.4 mg</td>
</tr>
</tbody>
</table>
Population approaches to Monitoring (Bayesian)

- Prior pop PK Values & variability
  - Patient covariates
  - Creatinine, wt., ht., gender)
- Estimate of PK in patient
- Revise estimate from level
- Review estimate of precision
- Generate estimate of Cmax and Cmin, along with dose

![Graph](image.png)
Audit of Practice - Gentamicin

- 50% of dose were less than local guidelines
- 88% of doses were outside of National guidelines
- 20% of sample draws were incorrectly timed
- 15% of doses adjusted on inadequate information or errors in interpretation
- 50% of AUCs were sub-optimal
- 20% of adequate therapy was adjusted

Martin, J. Clin Tox 2012
Organisation of TDM Services
Sample and information flows (Traditional)

Microbiology role
- Knowledge of infecting organism
- Black box to measure drug
- Interpret TDM results
- Advises clinician

Pharmacy roles
- Supports dosing
Organisation of TDM Services
Sample and information flows

“Information flows are frequently fractured and it is unclear who has oversight?”
TDM for Vancomycin

• First isolated 1953 and approved 1958
  – Pre 5-10 mg/L and Post 20-40 mg/L

• Rybak et al. Jan 2009. (AJHSP 66:82-98)*
  – Pre dose after 4th dose
  – Target exposure of AUC:MIC >400 (S.aureus)
  – <10 mg/L promotes resistance
  – 15-20 mg/L for isolate with MIC of 1mg/L
  – Loading dose of 25-30 mg/kg in serious sepsis (ABW)

*Infectious Diseases Society of America
American Society of Health-System Pharmacists
Society of Infectious Diseases Pharmacists
Use of the 2009 Consensus Guidelines

• 163 US hospital responses to survey
• Most now only use trough levels
• Most target levels >10 mg/L and 15-20 mg/L in complicated cases
• Few hospitals use loading doses
• Very few hospitals dose on the basis of ABW

Vancomycin Since 2009

- Kullar (CID 2011); Brown (AAC 2012); Holmes (AAC 2013)
  - AUC:MIC targets of 373-453

- Casapao (AAC 2013); Jacob (IJAA 2013)
  - High MIC (>1.5) associated with increased mortality and treatment failure

- VanHal (AAC 2013)
  - Nephrotoxicity risk increases with trough concentration and duration

- Cianferoni (Infection 2013); Norton (JAC 2014)
  - Continuous infusion levels >30 mg/L increase risk of AKI
Vancomycin TDM Post 2014

- Consensus Guidelines II in draft (2015/6)
  - Reaffirm AUC:MIC of >400
  - Confirm trough of 15-20mg/L in severe infection and extend to children
  - Loading algorithm for >2g and recommendations in obesity
  - Propose early monitoring (<24h)
  - Propose CI limit of 30 mg/L and closer monitoring
Summary

- Fundamental basis for dose optimisation of aminoglycosides is established
- Clear understanding of toxicity drivers
- Less clear understanding of efficacy drivers
- Clear need for greater individualised dosing & TDM; but how?
- Most TDM approaches adequately indentify over dosing of aminoglycosides but not under-dosing

“There was significant under-dosing and monitoring practices were haphazard”