AMINOGLYCOSIDES TDM

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OUTLINE

- Introduction about Aminoglycosides.
- Spectrum/uses.
- TDM
- Aminoglycosides TDM
- Pharmacodynamics
- Pharmacokinetics.
- Dosing in AG.
- Sampling time and Monitoring.
- Toxicity
- Cases
INTRODUCTION

• Aminoglycosides are widely used antibacterial agents, particularly for serious infections.

• They are bactericidal agents that inhibit protein synthesis.

• They have a narrow therapeutic index.
SPECTRUM/USES

• Single treatment for gm-ve bacilli.

• Empiric therapy.

• Combination with another drug for specific gm+ve infections, like Endocarditis.

• Combination with β-lactams.

• Surgical prophylaxis.
THERAPEUTIC DRUG MONITORING

To use drug concentrations to manage a patient's medication regimen and optimize the outcomes.
WHEN DO WE NEED TDM?

- Toxicity
- Lack of response
- Compliance assessment
- Changes in dose regimen
- Clinical state changes
- Drug interactions
- Efficacy
TDM IN AMINOGLYCOSIDES

• Narrow therapeutic index.
• Guide and monitor any dosing regimens.
• Evaluate for efficacy.
• Evaluate for potential toxicity.

Nephrotoxicity.
Ototoxicity.
PHARMACODYNAMICS

- A single dose of amikacin at 15 mg/kg
- Two doses of amikacin at 7.5 mg/kg each

Key points:
- Concentration (Conc)
- Peak
- Trough
- MIC
- Post Antibiotic Effect (PAE)

Post Antibiotic Effect occurs due to PAE.
PHARMACOKINETICS

Absorption:
- Poorly absorbed orally, given IV infusion or IM.

Distribution:
- Vd ranges from 0.2 -0.4 L/kg, and is increased in other conditions.
- High conc in urine, low in CSF, bile and bronchial secretions.

Elimination:
- Almost 99% is excreted unchanged by glomerular filtration.
- Half life (1.5 to 3.5 hrs).

Cystic fibrosis Vd = 0.35 L/kg
Ascites Vd = 0.32 L/kg

Prolonged in neonates, infants and reduced renal function.
Extended interval dosing (ODD):

- Concentration dependent antibiotics.
- Optimum bactericidal activity when conc 8-10 times the MIC.
- 7 mg/kg q24hrs. (Genta, Tobra)

Multiple daily dosing (traditional):

<table>
<thead>
<tr>
<th>CrCl</th>
<th>Dose (gentamicin, tobramycin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 ml/min</td>
<td>1.5-1.7 mg/kg/dose IV q8h</td>
</tr>
<tr>
<td>40-60 ml/min</td>
<td>1.2 - 1.5 mg/kg/dose IV q12h</td>
</tr>
<tr>
<td>20-40 ml/min</td>
<td>1.2-1.5 mg/kg/dose IV q12-24h</td>
</tr>
<tr>
<td>&lt;20 ml/min</td>
<td>2 mg/kg loading dose</td>
</tr>
</tbody>
</table>

Gram positive-synergy Dosing.

Exclusions!
Dosing:
• TBW in non-obese patients.
• AdjBW as the dosing weight in obese patients.
• Calculate CrCL with the Cockcroft-Gault equation.

Loading Dose:

<table>
<thead>
<tr>
<th>Site of infection or indication</th>
<th>Desired peak concentration</th>
<th>Loading dose, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated lower urinary tract infection, gram-positive endocarditis, synergy with beta-lactams for serious gram-positive infections</td>
<td>2 to 4 μg/mL</td>
<td>0.6 to 1.2</td>
</tr>
<tr>
<td>Gram-negative sepsis or other serious gram-negative infections</td>
<td>6 to 8 μg/mL</td>
<td>2.5</td>
</tr>
<tr>
<td>Gram-negative pneumonia or acute life-threatening gram-negative infection in a critically ill patient</td>
<td>7 to 9 μg/mL</td>
<td>3.0</td>
</tr>
</tbody>
</table>
**Maintenance Dose:**

### A. Gentamicin & Tobramycin Initial Dosing

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>High-Dose Extended-Interval* (Gentamicin/Tobramycin)</th>
<th>Conventional / Traditional (Gentamicin/Tobramycin)</th>
<th>Synergy** (Gentamicin/Tobramycin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>7 mg/kg Q24H</td>
<td>1.7 mg/kg Q8H</td>
<td>1 mg/kg Q8H</td>
</tr>
<tr>
<td>40-59</td>
<td>4 – 7 mg/kg Q36H</td>
<td>1.7 mg/kg Q12H</td>
<td>1 mg/kg Q12H</td>
</tr>
<tr>
<td>30-39</td>
<td>4 – 7 mg/kg Q48H</td>
<td>1.7 mg/kg Q24H</td>
<td>1 mg/kg Q24H</td>
</tr>
<tr>
<td>20-29</td>
<td>Not recommended</td>
<td>1.7 mg/kg Q24H</td>
<td>1 mg/kg Q24H</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Not recommended</td>
<td>2 mg/kg load, then dose by level</td>
<td>1 mg/kg load, then dose by level</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Not recommended</td>
<td>2 mg/kg load, then 1.5 mg/kg post-HD</td>
<td>1 mg/kg Q48-72H; consider redosing for pre-HD or post-HD Cp &lt; 1mg/L</td>
</tr>
<tr>
<td>CRRT</td>
<td>Not recommended</td>
<td>1.5 – 2.5 mg/kg Q24-48H</td>
<td>1 mg/kg Q24H, then by level</td>
</tr>
</tbody>
</table>

*See Hartford nomogram for monitoring of once-daily dosing regimens  
**Alternative for synergy: 3mg/kg Q24H for Streptococci and *Streptococcus bovis* endocarditis

### B. Amikacin Initial Dosing

<table>
<thead>
<tr>
<th>CrCL (mL/min)</th>
<th>High-Dose Extended-Interval* (Amikacin)</th>
<th>Conventional / Traditional (Amikacin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>15 – 20 mg/kg Q24H</td>
<td>5 – 7.5 mg/kg Q8H</td>
</tr>
<tr>
<td>40-59</td>
<td>15 mg/kg Q36H</td>
<td>5 – 7.5 mg/kg Q12H</td>
</tr>
<tr>
<td>30-39</td>
<td>15 mg/kg Q48H</td>
<td>5 – 7.5 mg/kg Q24H</td>
</tr>
<tr>
<td>20-29</td>
<td>Not recommended</td>
<td>5 mg/kg load, then dose by level</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Not recommended</td>
<td>5 – 7.5 mg/kg Q24H</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Not recommended</td>
<td>5 – 7.5 mg/kg post-HD</td>
</tr>
<tr>
<td>CRRT</td>
<td>Not recommended</td>
<td>10 mg/kg load, then 7.5 mg/kg Q24-48H</td>
</tr>
</tbody>
</table>

See Hartford nomogram for monitoring of once-daily dosing regimens- divide level by half then plot on graph
# SPECIAL POPULATIONS

<table>
<thead>
<tr>
<th>population</th>
<th>dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates, children</td>
<td><strong>0-7 days old:</strong> 4-5 mg/kg/day. <strong>Infants-children:</strong> 5-7.5 mg/kg/day.</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Supplemental doses of <a href="#">gentamicin</a> or <a href="#">tobramycin</a> of 1 to 2 mg/kg after each dialysis.</td>
</tr>
<tr>
<td>CRRT</td>
<td>LD= 2-3 mg/kg&lt;br&gt;MD= 1-2 mg/kg q48-72 hrs. “serum conc”</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>7.5-10.5 mg/kg/day “divided q8hr”</td>
</tr>
<tr>
<td>Burn patients</td>
<td>Doses up to 7 to 8 mg/kg per day.</td>
</tr>
<tr>
<td>Renal impairment “elderly”</td>
<td>According to CrCL “mentioned before”</td>
</tr>
</tbody>
</table>
SAMPLING TIME

• After three to five half-lives of the drug.

• Trough concentrations are measured within 30 minutes of the next dose.

• Peak concentrations within 30-60 minutes after the end of IV infusion, approximately 60 minutes after IM.
 LEVELS MONITORING

• Peak indicates efficacy.

• Trough indicates toxicity.

**Peak**
- Serious infections: 6-8 mcg/mL
- Life-threatening: 8-10 mcg/mL
- UTI: 4-6 mcg/ml
- Synergy: 3-5 mcg/mL

**Trough**
- Serious infection: 0.5-1 mcg/mL
- Life-threatening: 1-2 mcg/mL
- Hospital acquired pneumonia: <1 mcg/mL
INTERPRETATION + DOSE ADJUSTMENT

- Patient-specific pharmacokinetic parameters
- Serum conc. levels
- Optimal dose and frequency
## TOXICITY AND MANAGEMENT

<table>
<thead>
<tr>
<th>Side effect</th>
<th>comments</th>
</tr>
</thead>
</table>
| Nephrotoxicity         | • Estimated by 10-20%.  
• ODD vs conventional dosing.  
• Management.               |
| Ototoxicity            | • Can be irreversible.  
• cochlear and vestibular toxicity and disequilibrium.              |
| Neuromuscular Blockade | • Most patients have disease states or a drug therapy that interfere with neuromuscular transmission.  
• Myasthenia gravis is an absolute contraindication               |
CASE 1

A five years old female patient with a urinary tract infection being treated with Gentamicin 28 mg q 8hrs. She weighs 16 kg and 98 cm tall. Her serum Cr was 34. trough level came 0.4 mcg/L while peak level was 3 mcg/ml .. What’s your recommendation ?

• Keep the same dose/frequency.
• Switch to a OD dosing ( 7 mg/kg q 24= 112 mg q24)
• Increase dose on an 8 hourly frequency.
CASE 2

- A 55 years old male weighs 65 kg and 172 cm. Being treated with Tobramycin 110 mg q12 hrs (1.7 mg/kg) for Sepsis. Patient has serum Cr of 206, his peak level was 10 mcg/ml while trough level was 0.6 mcg/ml. Your recommendations will be:

  - Hold dose, resample for another level.
  - Decrease frequency to q 24 hrs with the same dose.
  - Decrease dose and frequency.
  - Do nothing.
THANK YOU

QUESTIONS?