AMINOGLYCOSIDE KINETICS

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AG Dosing Methods

1. Conventional Dosing
   - Traditional
   - Multiple dosing

2. Single daily
   - Once daily
   - High dose AG
   - Extended-interval dosing
Methods for AG Dosing

Conventional Dosing
  - Gent/tobra
    • 1 – 2 mg/kg IV q8hrs
  - Amikacin
    • 7.5 mg/kg IV q12hrs

Single Daily Dosing
  - Gent/tobra
    • 5 - 7 mg/kg IV q24hrs
  - Amikacin
    • 15mg/kg IV q24hrs

**For all AG dosing – Must account for renal function and potentially extend dosing interval for renal insufficiency**

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ODA vs. Traditional Dosing
Concentration-dependent bactericidal activity

Background:
- Positive and direct relationship between antibiotic concentration and bactericidal effect

Single Daily Dosing:
- Higher peak concentrations increase efficacy
  - Cpmax:MIC ratio 10:1
- Lower trough concentrations improve safety

Example:
- MIC of gentamicin vs. *P. aeruginosa* = 2 µg/mL
  - Traditional dosing = 10/2 = 5
  - Single daily dosing = 20/2 = 10
Postantibiotic Effect

Background:
- In vivo, PAEs 2 – 7 hours observed in neutropenic mice and 9 - 13 hours in normal mice
- Duration of PAE increases with longer exposure times and higher drug concentrations up to a maximal response

Single daily dosing
- Significant PAEs allows for longer dosing intervals
- PAE to maintain efficacy as concentrations fall below the MIC
Comparative Clinical Trials

Overall, most studies demonstrated
  – Similar efficacy
  – No significant difference in nephrotoxicity or ototoxicity
    • Audiometry not used in most studies

Patient populations
  – Most studies:
    • Gram-negative infections including UTIs, PID, intraabdominal, bacteremia, pneumonia
    • Limited data
    • Gram-positives, pediatric, pregnant, meningitis, osteomyelitis, dialysis patients, and burn patients
Econcomic Analysis

• Advantage of Single-daily Dosing
  – Simple dosage calculation
  – Fewer drug assays required
  – Reduced staff time in monitoring and administrating drug therapy
  – Fewer consumables used

Parker SE, Davey PG. PharmacoEconomics 1995;7:393-402
Single Daily AG Dosing

Fixed Dose Approach:

• Calculate an initial dose based on mg/kg (5-7 mg/kg)
  – Hartford, Barnes-Jewish
• Administer dose over an hour
• Draw a random level
  – NOT a peak or a trough
• Apply the level to a nomogram
Hartford Nomogram

Background:

- Goal: provide optimal PD parameters for common-organism with high MIC
  - *P. aeruginosa* with gentamicin MIC of 2.0µg/mL

- Achieve Cpmax = 20µg/mL
  - Cpmax:MIC = 20/2 = 10

- Drug-free interval
  - Cpmin <0.5 µg/mL for at least 4 hours
Hartford Nomogram

**Dose:** 7mg/kg

**Use IBW to calculate dose; if >20% above IBW, use adjusted body weight**

**Exclusion:** patients with altered or variable kinetics ie pediatric, pregnant, burn, ascites, dialysis patients

**Initial Dosing Interval:**

- CrCL > 60mL/min  q24hr
- CrCL > 40-59mL/min  q36hr
- CrCL > 20 – 39mL/min  q48hr
- CrCL < 20 mL/min serial levels to determine next dose
Hartford Nomogram

Monitoring:
  - Scr 2 – 3 times weekly
  - Obtain random concentration at 8 – 12 hours following 60 minute infusion unless meets the following criteria:
    - Criteria to withhold random concentration until day 5
      • Receiving ODA q24 hrs
      • Without concurrently administered nephrotoxic agents (amphotericin, cyclosporine, vanco)
      • Without exposure to contrast media
      • Not quadriplegics nor amputees
      • Not in the ICU
      • Less than 60 years old
Hartford Nomogram

![Nomogram Diagram](image)

- **Time (hours)**: 6, 7, 8, 9, 10, 11, 12, 13, 14
- **Concentration (mg/L)**: 14, 12, 10, 8, 6, 4, 2
- **Lines**:
  - **Q48h**: Red line
  - **Q36h**: Yellow line
  - **Q24h**: Green line
Example: Hartford

45 year old patient with positive blood cultures (preliminary report gram-negative rods) has been prescribed cefepime and gentamicin. Dose gentamicin per Hartford Nomogram.

Patient Demographics:
- 5’9”, wt=160 lbs, BUN/Scr=15/1.0
Example: Hartford

Patient Demographics

Actual body weight = 73 kg
Ideal body weight = 70.7
CrCL = 94 mL/min

Dose and interval

7mg/kg = 7 (70.7kg) = 495mg
500mg IV q24 hours
Example: Hartford

• After the first dose (500mg IV gentamicin); blood sample at 10hrs following the infusion was obtained.
  – Level = 4 µg/mL

• Is this appropriate?
Barnes-Jewish Hospital Nomogram

Initial dosage regimen
- Gentamicin 5mg/kg (round to nearest 50mg)
- Tobramycin 5mg/kg (round to nearest 50mg)
- Amikacin 15mg/kg (round to nearest 50mg)

** Use IBW to calculate dose; if >20% above IBW, use adjusted body weight

Exclusions: Not recommended in pregnancy, dialysis, endocarditis, CrCL<20mL/min, cystic fibrosis, mycobacterial infections, infants, > 20% BSA burns

CID 1997;24:786-95
Barnes-Jewish Hospital Nomogram

Initial Dosing Interval:

- CrCL $\geq$ 60mL/min  q24hr
- CrCL > 40-59mL/min  q36hr
- CrCL > 20 – 39mL/min  q48hr
- CrCL < 20mL/min  traditional dosing
Barnes-Jewish Hospital Nomogram

Monitoring:

– Obtain mid-interval drug level 8 – 12 hours after initial dose
  • Evaluate interval based upon nomogram
– Repeat drug level 1 – 2 times weekly
– Repeat Scr 2 – 3 times weekly
– Patient with fluid shifts may need more frequent monitoring
Barnes-Jewish Nomogram

Time (hours)

Concentration (mg/L)

q24h
q36h
q48h
Barnes-Jewish Hospital Nomogram

Undetectable level
  – If 8 - 12 hr level is undetectable and infection is not responding, consider traditional dosing
Fixed Dose Approach

Criticism

– Not adjusted for infection type
– Not individualized based upon kinetic properties
– Administered to patients with renal insufficiency
Individualized Single Daily AG

Individualize Single daily dosing using patient specific and target serum concentrations

– Optimize PD parameters
– Minimize unnecessary excess exposure

**Desired Concentrations: Single Daily Dosing**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gent/tobra</th>
<th>Amikacin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>10 – 12</td>
<td>60 – 70</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>16 – 20</td>
<td>60 – 70</td>
</tr>
<tr>
<td>Cystitis</td>
<td>6 – 8</td>
<td>40 – 50</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>12 – 14</td>
<td>60 – 70</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>12 – 16</td>
<td>60 – 70</td>
</tr>
</tbody>
</table>

**Trough Concentrations**

- **Gent/tobra**: <0.3
- **Amikacin**: <5
Individualized Single Daily AG

Individualized PK using patient-specific data
- Weight, renal function, Vd, Ke, and infection type

Exclude:
- CrCL<50mL/min; age >70 years old
- Patients with burn or spinal cord injury, meningitis, endocarditis, or enterococcal infections
## Individualized Single Daily AG

<table>
<thead>
<tr>
<th></th>
<th>ODA (n=200)</th>
<th>TDA (n=100)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>$C_{max}$:MIC</strong></td>
<td>12.6 ± 4.9</td>
<td>5.8 ± 2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>$\text{AUC}_{24}$:MIC</strong></td>
<td>56.5 ± 24.8</td>
<td>52.3 ± 23.6</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Cumulative AUC</strong></td>
<td>561 ± 506.9</td>
<td>691.4 ± 454</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Duration of therapy</strong></td>
<td>8.4 ± 5.4</td>
<td>9.8 ± 5.1</td>
<td>0.04</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nephrotoxicity</th>
<th>ODA</th>
<th>TDA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable pts</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>187 (94)</td>
<td>95 (95)</td>
<td>NA</td>
</tr>
<tr>
<td>Toxicity</td>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 (7.5)</td>
<td>14 (14.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Change in Scr</td>
<td>mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.36 ± 0.79</td>
<td>0.57 ± 1.1</td>
<td>0.15 27</td>
</tr>
</tbody>
</table>
### Individualized Single Daily AG

#### Factors related to Nephrotoxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-24h}$</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$\text{Cmin}$</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Length of AG therapy</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cumulative AUC</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Vancomycin use</td>
<td>0.04</td>
</tr>
<tr>
<td>Other nephrotoxins</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Individualized Single Daily AG

- Dose to attain target peak for appropriate disease states
- Verify Cmax:MIC ratio > 8 whenever possible
- Exclude patients with
  - Age > 70 years old
  - CLcr<50mL/min
  - Estimated/calculated or actual trough > 0.25mg/L
Example

SL is a 59 yo male admitted to the hospital 3 weeks ago and now diagnosed with hospital-acquired pneumonia. Would piperacillin 3g IV q4 and tobramycin 400mg IV q24 hours be appropriate regimen?

Patient Demographics:
- 5’10”, 160lbs, BUN/Scr=22/1.8mg/dL
- Sputum culture: *P. aeruginosa*; tobramycin=1.0µg/mL
Summary

• Understand the principles of ODA

• Be able to provide appropriate dosing regimens and monitoring parameters for ODA and traditional AG