Single Daily Dosing of Aminoglycosides:

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Objectives

- Define from a clinical perspective what is meant by the term single daily dosing of aminoglycosides.
- Provide the rationale used for using a SDD vs a conventional strategy for administering aminoglycosides.
- Provide the rationale used by the Hartford group in designing their 7 mg/kg/d SDD therapeutic recommendation.
- Identify what is currently believed to be the appropriate pharmacodynamic outcome predictor for aminoglycosides and an appropriate range of values for this parameter. Also identify any clinical shortcomings in how these data have been applied to SDD dosing strategies.
- Define what is meant by an aminoglycoside free interval and how the PAE concept applies to extending aminoglycoside dosing intervals.
- Define what is meant by adaptive resistance and how this concept applies to SDD aminoglycoside dosing strategy.
- Provide 3 situations where a SDD strategy for aminoglycosides might not be appropriate.
Single Daily Dosing of Aminoglycosides

Introduction

- SDD would seem to be self defining
- Dose ranges from 3 to 7 mg/Kg/day for gentamicin and tobramycin
- “Daily” dose depending on method ranges from Q 12, 24, 36, to 48 H
Single Daily Dosing of Aminoglycosides

Moore et. al. JID 155:93

- Maximal response seen as \( \text{Cpx(1hr post)} : \text{MIC ratio} \approx 10 \)
- Majority patients studied had urosepsis
- Patients not necessarily individualized to targeted peak & troughs for > 72 hr
SDD Rationale

- Maximize the effect of concentration dependent killing
  - Optimize Cpx : MIC ratio
    - Increases the rate of bacterial kill
    - Increases the extent of bacterial kill
    - May extend PAE
Concentration Dependent Killing

Aminoglycosides
Fluoroquinolones
Metronidazole
Bacterial Concentration Kill Curve & Concentration Dependent Killing

- CFU/ml
- Time

- 10^7 CFU/ml
- 7mg/Kg
- Cpx =25 mg/L
- 1.5mg/Kg
- Cpx =7 mg/L
Post Antibiotic Effect (PAE)

Aminoglycosides
Post Antibiotic Effect (PAE)

- **Method**
  - Fixed inoculum exposed to a specific concentration of antibiotic for a defined period of time
  - Bacteria are washed and suspended in fresh media and allowed to grow
  - Difference in time for 1 log growth as compared to control is defined as PAE
  - PAE may wane over time for AG’s
Post Antibiotic Effect (PAE)

- Antibiotic, species, & organism dependent phenomena
- Extremely variable parameter among same species of organism
- Usually measured following a single antibiotic exposure
- Not a routine laboratory test
- Difficult concept to incorporate into a dosing scheme
SDD Rationale

- Produce an Aminoglycoside Free Interval
  - Limits tissue accumulation
  - Overcomes adaptive resistance
  - Required time frame yet undefined
Aminoglycoside Transport

Blood & Tissue Equilibrium

Blood Compartment

Tissue Compartment

Saturable

Cp

Ct
Aminoglycoside Resistance

- **Stable Resistance**
  - Enzyme mediated

- **Environmental Resistance**
  - Level of O2 tension, pH, + Calcium or Magnesium

- **Unstable or Adaptive Resistance**
  - Control of AG uptake or transport
Aminoglycoside Transport

Gram Negative Pathogen

- Passive Ionic Binding
- Energy Dependent Transport

Gentamicin

Effect
- Concentration Dependent

Time Frame
- 2 Hours
- Rapid Kill

Concentration Independent
- 2 to 6 Hours
- Slow Kill
Single Daily Dosing of Aminoglycosides

- Clinical studies to date (N~ 40) compare SDD vs conventional therapy
  - Virtually all underpowered to show difference in efficacy or toxicity
- SDD attempts to produce high Cpx’s in all patients for every infection
- SDD does not address the diversity in patient pharmacokinetic parameters
- No Studies have attempted to optimize the Cpx : MIC ratio
Single Daily Dose Therapy

- **Efficacy Studies**
  - Most often a bacterial pathogen not recovered
  - Most patients receive other effective antibiotics + surgery
    - Confounding variables makes outcome interpretation difficult
Hartford SDD Program

Nicolau, DP et al AAC 39:650-655, 1995
Hartford Program Rationale
Nicolau, DP et al AAC 39:650-655, 1995

- Goal is to produce Cpx : MIC ratio > 10
- Based on worst case scenario
  \[ P. \text{aeruginosa} \ \text{MIC-50} = 2\text{mg/L} \]
- To produce Cpx = 20 mg/L requires 7 mg/Kg/day
Hartford Program

- Rather than *P. aeruginosa*, patient likely to have:
  - No Bacterial Pathogen
  - Gram Positive Pathogen
  - Gram Negative Pathogen with MIC < 0.5 mg/L
  - If Cpx = 20 mg/L, Ratio > 40
Hartford Program

Had the investigators used the same rationale but

- Substituted tobramycin for gentamicin
  - Tobramycin MIC 25 - 50% lower
- Recommended dose would be
  1.75 to 3.5 mg/Kg/day rather than 7 mg/Kg/Day
Distribution Phase with SDD
Demczar et al Abstract 103 36th ICAAC 1996

- Alpha phase
- Beta phase
- 7 mg/Kg
- 1.5 mg/Kg

Time

Was the appropriate pharmacokinetic model used to construct the nomogram?

Is 7 mg/Kg the appropriate dose?
Single Daily Dose Therapy Case

**Pneumonia with gram negative MIC = 2mg/L**

- **Peak = 30 mg/L**
- **Conc (lung) < 15mg/L**
  - Assumes 30 to 50% AG lung penetration
- **Peak : MIC Ratio = 15**
- **Conc (lung) : MIC ratio < 7.5**
Single Daily Dose Therapy Case

- **Urosepsis with** gram
  negative MIC < 0.5 mg/L

  - Peak = 7 mg/L
  - Conc (urinary tract) = Very High
  - Peak : MIC Ratio > 14
  - Conc (urinary tract) : MIC ratio = Huge
Hartford Program Unknowns

- Will 24 hr or extended dosage intervals prevent tissue accumulation?
- Would hypermetabolic patients benefit from more frequent dosing?
- Is the goal a peak = 20 mg/ L in all patients or a peak : MIC ratio > 10?
Single Daily Dose Therapy

Unknowns

- Optimal pharmacodynamic outcome parameter
- Optimal value for predictor by site of infection
- Optimal duration of aminoglycoside free period
# SDD Serum Sampling Policies

<table>
<thead>
<tr>
<th>Option</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No levels:</td>
<td>Potential liability</td>
</tr>
<tr>
<td>One Level 6-8 hrs post:</td>
<td>Provides no PK data</td>
</tr>
<tr>
<td>High:</td>
<td>&gt; t1/2, &lt; Vd, RN error</td>
</tr>
<tr>
<td>Low:</td>
<td>&lt; t1/2, &gt;Vd, RN error</td>
</tr>
<tr>
<td>Trough/Peak:</td>
<td>Cpn ~ 0mg/L</td>
</tr>
<tr>
<td>PK Study:</td>
<td>Can be done with 2 levels</td>
</tr>
<tr>
<td></td>
<td>Provides PK data</td>
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</tbody>
</table>

Peak, Trough, & Cpmax /MIC Outcomes with SDD Therapy

Integration of information:
- Patient pharmacokinetics
- Drug pharmacodynamics
- Pathogen sensitivity
Aminoglycoside Pharmacokinetic Parameters  Zaske, DE et al AAC 21:407,1982

1,640 aminoglycoside patients with normal renal function

- Half-life range < 1 to >12 hours
  - Short t1/2 have Cp-min ~ 0 mg/L for > 12 hrs
  - Long t1/2 never approach Cp-min ~ 0 mg/L
- Distribution volume range < 0.1 to > 0.6 L/Kg
  - Small Vd have Cp-max > 20 mg/L
  - Large Vd have Cp-max < 20 mg/L
### Steady State Cpx & Cpn’s on 6 mg/Kg

<table>
<thead>
<tr>
<th>$T_1/2$ (hr)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_d$ (L/Kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>51/0</td>
<td>56/1</td>
<td>60/4</td>
<td>78/21</td>
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<tr>
<td>0.2</td>
<td>25/0</td>
<td>28/&lt;1</td>
<td>30/2</td>
<td>39/10</td>
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<tr>
<td>0.3</td>
<td>17/0</td>
<td>19/&lt;1</td>
<td>20/1</td>
<td>26/7</td>
</tr>
<tr>
<td>0.4</td>
<td>13/0</td>
<td>14/&lt;1</td>
<td>15/1</td>
<td>19/5</td>
</tr>
<tr>
<td>0.6</td>
<td>8.5/0</td>
<td>9/&lt;1</td>
<td>10/&lt;1</td>
<td>13/3</td>
</tr>
</tbody>
</table>

Aminoglycoside Manufacturing
Lot to Lot Variability

- USP provides for a manufacturing tolerance in the production of aminoglycosides
- Nahata et al reported that gentamicin labeled to contain 80mg of gentamicin actually yielded 107mg of drug
- 7 mg/Kg doses of gentamicin may actually deliver substantially more drug

Nahata, M: Ther Drug Monitoring 8: 256, 1986
Single Daily Dosing of Aminoglycosides

- Arbitrary Assumptions for Pharmacodynamic Simulation
  - Want Cpx : MIC ratio
    - >10 but < 20
  - Want Cpn < 2 mg/L
    - > 4 hours but < 12 hours
## Cpeak / MIC Ratio & Time < 2 mg/L

Pathogen MIC = 0.5 mg/L

<table>
<thead>
<tr>
<th>T1/2 (hr)</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>12</th>
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</thead>
<tbody>
<tr>
<td><strong>Vd (L/Kg)</strong></td>
<td><strong>101/14112/4</strong></td>
<td><strong>121/0</strong></td>
<td><strong>155/0</strong></td>
<td><strong>78/0</strong></td>
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<tr>
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<td>51/16</td>
<td>56/8</td>
<td>60/0</td>
<td>78/0</td>
</tr>
<tr>
<td>0.2</td>
<td>34/17</td>
<td>37/10</td>
<td>40/3</td>
<td>52/0</td>
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<tr>
<td>0.3</td>
<td>25/18</td>
<td>28/12</td>
<td>30/6</td>
<td>39/0</td>
</tr>
<tr>
<td>0.4</td>
<td>17/19</td>
<td>19/14</td>
<td>20/9</td>
<td>26/0</td>
</tr>
</tbody>
</table>

### Cpeak / MIC Ratio & Time < 2 mg/L

**Pathogen MIC = 4 mg/L**

<table>
<thead>
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<th>$T_{1/2}$ (hr)</th>
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<th>6</th>
<th>12</th>
</tr>
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<tbody>
<tr>
<td>$V_d$ (L/Kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>13/14</td>
<td>14/4</td>
<td>15/0</td>
<td>19/0</td>
</tr>
<tr>
<td>0.2</td>
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<td>7/8</td>
<td>8/0</td>
<td>10/0</td>
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<tr>
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<td>0.4</td>
<td>3/18</td>
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<td>5/0</td>
</tr>
<tr>
<td>0.6</td>
<td>2/19</td>
<td>2/14</td>
<td>3/9</td>
<td>3/0</td>
</tr>
</tbody>
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Single Daily Dosing of Aminoglycosides

- SDD Relative Contraindications:
  - Half-life > 4 Hours
  - Bacterial MIC > 2 mg/L
  - *S. aureus* or Enterococcal infections
  - Bacterial pneumonia with pathogen having high MIC
Toxicity with Single Daily Dose
Aminoglycoside Therapy
Endotoxin Like Reactions with SDD Aminoglycoside Therapy

- Approximately 40 patients receiving 7 mg/Kg/d of gentamicin developed rigors, fever, tachycardia, &/or a decrease of > 20mm Hg SBP within 3 hrs of dose.
- Pyrogenic reactions seen with > 5 EU/Kg.
- 7mg/Kg = 5.6 EU/Kg.
- Approximately 28% of aminoglycoside therapy in USA is SDD.

MMWR 47(41):877-880, 1998
Ototoxicity Toxicity
Singer C et al AAC 40:2209, 1996

- 10% (3/33 patients) developed vestibular dysfunction on 6 mg/kg/d
  - 52yr, calCrCl=71ml/min, ~4wks therapy
  - 72yr, calCrCl=72ml/min, ~6wks therapy
  - 80yr, calCrCl=57ml/min, ~2wks therapy

- Desired Cpx ~ 20mg/L  Cpn < 0.5 mg/L
Single Daily Dosing of Aminoglycosides

**Conclusions**

- SDD not for every infection, pathogen, or patient
- Must have therapeutic goal based on pathogen susceptibility and location of infection
- PK’s remains a useful tool to screen patients and to establish desired Cpx : MIC ratio