Single Daily Dosing of Aminoglycosides

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Aminoglycosides

- Goal of therapy
  - Dose is sufficient to kill suspected pathogen
  - Dose has low probability of adverse drug reaction
- What is SDD or ODA?
  - Moving target in the literature
    - Gentamicin & tobramycin dose ranges from 3 to 10 mg/Kg/day
    - The “Daily” dose depending on method and renal function (Q 12, 24, 36, to 48 H)

First Part of SDD Rationale

- Maximize concentration dependent killing
  - Optimize Peak : MIC ratio
    - Increases the rate of bacterial kill
    - Aminoglycosides may be concentration dependent killers of Gram negatives
    - Data unclear for staphylococci, streptococci, enterococci, and mycobacterium
    - Increases the extent of bacterial kill
    - Percent of bacterial population killed over time
    - May extend PAE
    - Magnitude of effect vary by & within species
    - Bacteria may develop tolerance over time

Second Part of SDD Rationale

- Create a drug free interval to overcome:
  - Adaptive resistance
  - Drug accumulation & toxicity
  - Desired magnitude of this interval is unknown

Aminoglycoside Transport

- Gram Negative Pathogen
- Passive Ionic Binding
- Energy Dependent Transport
- Gentamicin
- Effect: Concentration Dependent
- Time Frame: 2 Hours Rapid Kill
- Gentamicin
- Effect: Concentration Independent
- Time Frame: 2 to 6 Hours Slow Kill

Moore et. al. JID 155:93
- Maximal response seen as Peak(1hr post) : MIC ratio – 10
- Majority patients studied had urosepsis
- Patients not necessarily individualized to targeted peak & troughs for >72 hr
- These data serve as foundation for 10 X MIC SDD rationale
Aminoglycoside Transport

Blood & Tissue Equilibrium

Blood Compartment  Tissue Compartment

Saturable

Cp  Ct

Bacterial Concentration Kill Curve & Concentration Dependent Killing

Bacterial Infection

Burden  ~10^7-9 CFU/ml

Gm

CFU/ml

MDD

1.5mg/Kg

Cpx = 6-8 mg/L

MIC = 0.5 mg/L

MIC = 0.5 mg/L

SDD

7mg/Kg

Cpx = 20-25 mg/L

MIC = 2 mg/L

MIC = 0.5 mg/L

Time

What is the Therapeutic Goal for SDD?

- Peak gentamicin concentration 20 mg/L in all patients?
- Peak : MIC ratio ≥ 10 in all patients?
- Are these two goals conflicting or complimentary?

Hartford Program Rationale

- Based on worst case scenario of *P. aeruginosa* with gentamicin MIC_{90} = 2mg/L.
- To produce Peak = 20 mg/L requires dose of 7 mg/Kg/day (based on 1 compartment model).
- Had the investigators used the same rationale but:
  - Substituted tobramycin for gentamicin
  - For *P. aeruginosa*, tobramycin MIC ≥ 1 tube dilution lower
  - Recommended dose would be ≤ 3.5 vs 7 mg/Kg/day

Single Daily Dosing of Aminoglycosides

- Clinical studies & meta analysis to date compare SDD vs conventional multiple daily dose (MDD)
  - Virtually all studies underpowered for efficacy or toxicity
  - No clear trend evident other than SDD ~ MDD
- SDD attempts to produce high peaks in all patients for every infection
- No studies have attempted to optimize the Peak/MIC ratio vs SDD
- SDD does not address the diversity in patient pharmacokinetic parameters

Distribution Phase with Higher Doses

Demczar et al Abstract 103 36th ICAAC 1996

- 7 mg/Kg
- Was the appropriate pharmacokinetic model used to construct the nomogram?
- Is 7 mg/Kg the appropriate dose?
- 1.5 mg/Kg
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 serum peak = 20 mg/L; peak : MIC ratio ≥ 40
  - Concentrations & ratios higher or lower in other sites
- Most physicians capable of identifying situations where probability of *P. aeruginosa* is high

7 mg/Kg/day Peak / MIC Ratio
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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<tr>
<td>Vd (L/Kg)</td>
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</tbody>
</table>

Adapted Rotschafer, JC et. al. Pharmacother 12(6 Pt2):64S-70S, 1992

7 mg/Kg/day Peak / MIC Ratio
Pathogen MIC = 4 mg/L

<table>
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<td>Vd (L/Kg)</td>
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</table>

Adapted Rotschafer, JC et. al. Pharmacother 12(6 Pt2):64S-70S, 1992

Gentamicin or Tobramycin
Steady State Cpx & Cpn’s on 7 mg/Kg

<table>
<thead>
<tr>
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<th>12</th>
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<tbody>
<tr>
<td>Vd (L/Kg)</td>
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<tr>
<td>0.6</td>
<td>10/0</td>
<td>10/1</td>
<td>12/1</td>
<td>15/4</td>
</tr>
</tbody>
</table>

Once T1/2 ≥ 4 hrs essentially no drug free interval

Adapted Rotschafer, JC et. al. Pharmacother 12(6 Pt2):64S-70S, 1992

Single Daily Dose Therapy Case
Gram Negative Pneumonia

- Gram negative pathogen MIC = 2 mg/L
  - Aminoglycoside Peak = 20 mg/L
  - Aminoglycoside conc (lung) ≤ 10 mg/L
  - Assumes 30 to 50% lung penetration
  - Peak : MIC Ratio = 10
  - Conc (lung) : MIC Ratio ≤ 5

Single Daily Dose Therapy Case
Urinary Tract Infection

- Gram negative MIC ≤ 0.5 mg/L
  - Aminoglycoside Peak = 7 mg/L
  - Conc (urinary tract) = Very High
  - Peak : MIC Ratio ≥ 14
  - Conc (urinary tract) : MIC ratio = Huge
Ototoxicity & Nephrotoxicity Risks

- Elderly
- Renal dysfunction
- Elevated peak concentrations (Ototoxicity)
- Elevated trough concentrations (Nephrotoxicity)
- Extended therapy
- Genetic risk for ototoxicity
  - Maternally transmitted gene trait that causes hypersensitivity to AG
  - Mitochondrial DNA polymorphism 1555 position on 12S mt rRNA mutated to a G

Aminoglycoside Toxicity: Daily vs Thrice Weekly Dosing for Treatment of Mycobacterial Disease
Peloquin, CA et al CID 38:1538-1544, 2004

- 87 patients receiving streptomycin, kanamycin, or amikacin randomized to receive:
  - 15 mg/Kg QD (Cp_max 35-45 mg/L)
  - 25 mg/Kg Three times a week (Cp_max 65-80 mg/L)

<table>
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<tr>
<th></th>
<th>Streptomycin</th>
<th>Kanamycin</th>
<th>Amikacin</th>
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<td>11</td>
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<tr>
<td>Ototoxicity</td>
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<tr>
<td>Nephrotoxicity</td>
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<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Vestibular</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>+ Nystagmus test</td>
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<tr>
<td>+ Romberg</td>
<td>2</td>
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<tr>
<td>+ Heel to toe</td>
<td>4</td>
<td>0</td>
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</tr>
</tbody>
</table>

- Dose and frequency not associated with toxicity

Aminoglycoside Toxicity: Daily vs Thrice Weekly Dosing for Treatment of Mycobacterial Disease
Peloquin, CA et al CID 38:1538-1544, 2004

SDD Serum Sampling Policies

<table>
<thead>
<tr>
<th>Option</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>No levels:</td>
<td>Potential liability</td>
</tr>
<tr>
<td>High:</td>
<td>Provides no PK data</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 &amp; provides PK data</td>
</tr>
</tbody>
</table>

Confounding Variables in SDD Studies

- Studies include:
  - Mixed patient populations
  - Patients with no documented pathogen or a variety of pathogens and infections examined collectively
  - MDD group likely optimized (Peak/MIC ratio) in many infections
  - Include different aminoglycosides & doses
  - Different institutions and standard of care
  - Different inclusion criteria
  - Different definitions of toxicity
- Difficult to tease out the importance of the aminoglycoside dosing method in this background

Single Daily Dosing of Aminoglycosides
Relative Contraindications?

- SDD Relative Contraindications:
  - Long term therapy (Endocarditis or Osteomyelitis)
  - Half-life > 4 Hours
  - Elderly
  - Patients with compromised renal function
  - Adjunct Therapy
  - S. aureus & enterococci
  - Bacterial pathogen MIC > 2 mg/L
  - Mycobacterial infections
  - Bacterial pneumonia with pathogen having high MIC
  - Most urinary tract infections
  - Pregnancy
Other Issues with SDD

Lot to lot manufacturing variability which is exaggerated by SDD
- Does 1cc ~ 40 mg of gentamicin or tobramycin?

Previous issues with endotoxin like reactions which is also exaggerated with SDD

Nephrotoxicity and Ototoxicity are still very real issues that have not gone away with SDD

Appropriate monitoring
- Especially with home therapy
- Long term therapy

Is once a day better than multiple daily doses or pharmacokinetic monitoring?

Question will likely go unanswered:
- Aminoglycosides used less frequently vs fluoroquinolones
  - Aminoglycosides are used for shorter duration of time
  - Many patients have peak:MIC ratio optimized whether using MDD or SDD
  - Aminoglycosides are generic drugs & industry unlikely to sponsor trials with sufficient power to detect differences in dosing method

Single Daily Dosing (SDD) of Aminoglycosides

Conclusions
- SDD not for every infection, pathogen, or patient
- SDD has not eliminated aminoglycoside ADR's
- Still must have therapeutic goal based on pathogen susceptibility and location of infection
- Pharmacokinetics remains a useful tool to screen patients & to establish an optimal Cp-max : MIC ratio