

Single Daily Dosing of Aminoglycosides

John C. Rotschafer, Pharm D, FCCP
Professor
College of Pharmacy
University of Minnesota

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.

Aminoglycosides

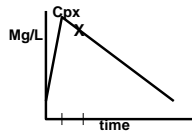
- **Goal of therapy**
 - Dose is sufficient to kill suspected pathogen
 - Dose has low probability of adverse drug reaction
- **What is SDD or ODA?**
 - **Moving target in the literature**
 - Gentamicin & tobramycin dose ranges from 3 to 10 mg/Kg/day
 - The "Daily" dose depending on method and renal 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

Single Daily Dosing of Aminoglycosides

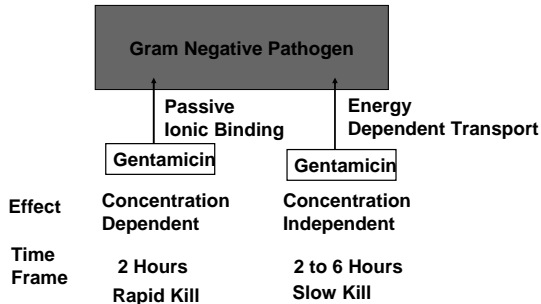
- Moore et. al. JID 155:93
 - Maximal response seen as Peak(1hr post) : MIC ratio ~ 10
 - Majority patients studied had urosepsis
 - Patients not necessarily individualized to targeted peak & troughs for ≥ 72 hr
 - These data serve as foundation for 10 X MIC SDD rationale



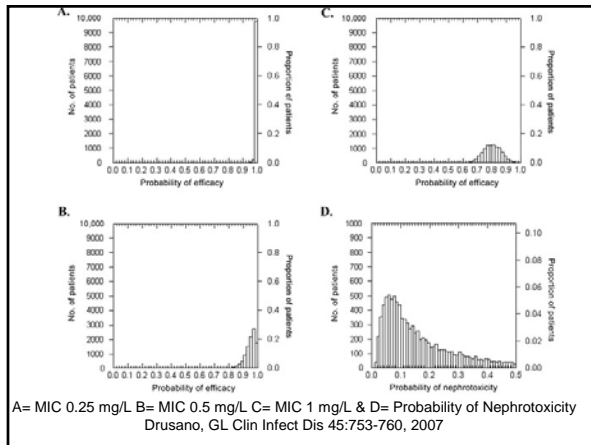
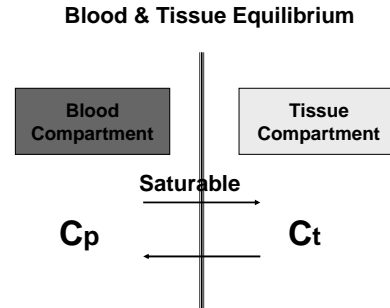
Second Part of SDD Rationale

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

Aminoglycoside Transport



Aminoglycoside Transport



Single Daily Dosing of Aminoglycosides

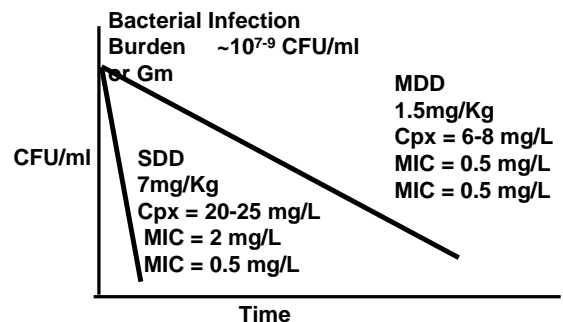
- Clinical studies & meta analysis to date compare SDD vs conventional multiple daily dose (MDD)
 - Virtually all studies underpowered for efficacy or toxicity
 - No clear trend evident other than SDD ~ MDD
- SDD attempts to produce high peaks in all patients for every infection
- No studies have attempted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

Wide variation in single, daily-dose aminoglycoside pharmacokinetics in patient with burn injuries

Klein LL et al J Burn Care Rehabil 18:116-124, 1997

- 52 Burn patients receiving gentamicin or tobramycin studied retrospectively to determine peaks & troughs
- 40/52 (77%) had CrCl > 60 ml/min
 - Could not use SDD in 12/52 patients
- Extreme variability in peak and trough concentrations
- Average time to reach 0.1 mg/L 16 hours

Bacterial Concentration Kill Curve & Concentration Dependent Killing



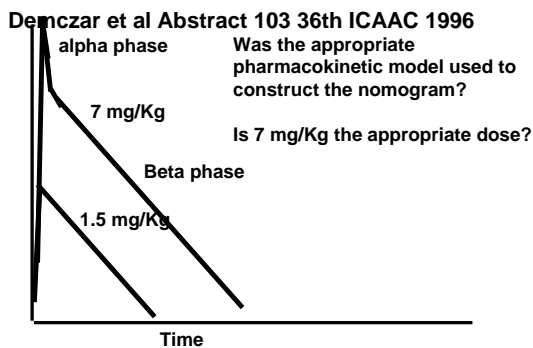
What is the Therapeutic Goal for SDD?

- 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 MIC₅₀= 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

Distribution Phase with Higher Doses



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

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

T1/2 (hr)	2	4	6	12
Vd (L/Kg)				
0.1	59/0	65/1	70/5	91/25
0.2	29/0	33/<1	35/2	45/12
0.3	20/0	22/<1	23/2	30/8
0.4	15/0	16/<1	17/1	22/6
0.6	10/0	10/<1	12/<1	15/4

Once t1/2 ≥ 4 hrs essentially no drug free interval

Adapted Rotschafer, JC et. al. Pharmacother 12(6 Pt2):64S-70S, 1992
Zaske, DE et al AAC 21:407,1982

7 mg/Kg/day Peak / MIC Ratio

Pathogen MIC = 0.5 mg/L

T1/2 (hr)	2	4	6	12
Vd (L/Kg)				
0.1	118	130	140	182
0.2	58	66	70	90
0.3	40	44	46	60
0.4	30	32	34	44
0.6	20	20	24	30

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

7 mg/Kg/day Peak / MIC Ratio

Pathogen MIC = 4 mg/L

T1/2(hr)	2	4	6	12
Vd(L/Kg)				
0.1	15	16	18	23
0.2	7	8	9	11
0.3	5	6	6	8
0.4	4	4	4	6
0.6	3	3	3	4

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
- Hutchin, T. et al Nucleic Acids Research 21:4174-4179, 1993
Fischel-Ghodsian N et al Am J Otolaryngol. 14(6):399-403, 1993

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 (C_{p,max} 35-45 mg/L)
 - 25 mg/Kg Three times a week (C_{p,max} 65-80 mg/L)
- Auditory (250-8000 Hz) and vestibular testing

N	Streptomycin		Kanamycin		Amikacin	
	QD	3X	QD	3X	QD	3X
	(16)	(16)	(16)	(17)	(11)	(11)
Ototoxicity	3	3	7	7	7	5
Vestibular	1	2	2	2	1	0
Nephrotox	2	4	0	3	3	1

- 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

ADR	No. (%) Patients		
	< 4wks	5-8wks	>8wks
	n=87	n=82	n=77
Nephrotoxicity	3(3)	2(2)	8(10)
Ototoxicity	7(8)	8(10)	17(22)
+ Nystagmus test	3(3)	0(0)	0(0)
+ Romberg	2(2)	0(0)	0(0)
+ Heel to toe	4(5)	0(0)	0(0)

- Ototoxicity independent of nephrotoxicity or vestibular toxicity
- Ototoxicity not associated with size of frequency of dose

SDD Serum Sampling Policies

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

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 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
 - Gentamicin or Tobramycin MIC > 2 mg/L
 - Mycobacterial infections
 - National Jewish is using SDD or QOD for 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 SDD better than MDD 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

Is SDD better than MDD or pharmacokinetic monitoring?

- **Question will likely go unanswered:**
 - Clinicians less likely to publish their experiences with aminoglycosides today as opposed to past
 - Difficult to identify the role dosing methods play in background of medical/surgical care, other antibiotics, & the presence of aminoglycosides in both study arms
 - If SDD really makes a difference in efficacy &/or toxicity, the data should be showing a clear trend

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