Review of the Pharmacodynamic Principles that Determine the Dosing and Monitoring of Aminoglycosides

Memorial Health Care System
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Objectives

1. Identify the indications for aminoglycoside therapy.
2. Differentiate pharmacokinetic/pharmacodynamic differences among aminoglycosides.
3. Discuss dosing strategies based on pharmacodynamic principles.
4. Discuss monitoring parameters and the use of dosing nomograms.
5. Identify the possible toxicities of aminoglycosides.

FDA Approved Aminoglycosides[1]

- **Amikacin**
- **Gentamicin**
- **Tobramycin**
- Streptomycin
- Neomycin
- Paromomycin

Mechanism of Action

- Bind to 16S ribosomal RNA of the 30S ribosomal subunit
  - Prevents elongation

When do we use Aminoglycosides?[2]

- Empiric treatment of gram negative sepsis
- Pseudomonal infections
- Synergy with cell wall active agents in gram positive infections
  - Eg: endocarditis

- Activity?[3]
  - Amikacin has the broadest activity
  - Tobramycin has greater susceptibility to pseudomonas than gentamicin

Aminoglycoside Kinetics[2]

		Elimination Half-life	
Agent	**Volume of Distribution**	**Normal**	**CrCl < 10 ml/min**
Amikacin	0.3	2.5-3	30
Gentamicin	0.22-0.3	2.5-3	30-50
Tobramycin	0.33	2.5-3	56
Streptomycin		2.5	100

- Where do AMGs distribute?
  - Good – body fluids (synovial, peritoneal, ascitic, pleural)
  - Poor – CNS and vitreous
  - Slowly – bile, feces, prostate, amniotic fluid
- Protein binding of almost all AMGs < 10%

Abnormal Situations[2]

- In what situations would you have a higher V_d and lower peak levels?
  - Sepsis
  - Fever – includes febrile neutropenia
  - Severe burns
  - Congestive cardiac failure
  - Peritonitis
  - Immediate postpartum period
  - Parenteral nutrition

AMG Clearance[2]

- Renal utilizing glomerular filtration
  - Decreased in poor renal function
  - As a result – also decreased in the elderly and neonatal populations
- In patients with ESRD what type of clearance is most utilized?
  - Non-renal clearance
- Can HD, CRRT or PD remove AMGs?[1]

Rapid Clearance of AMGs[2]

- In what patients is AMG clearance most rapid?
  - Children
  - Pregnancy
  - Immediately postpartum
  - Cystic fibrosis

Characteristics of AMGs

- Bactericidal[2]
- Concentration dependant killing[2]
- PAE – usually 2-4 hours[2]
  - Gram negative > gram positive[1]
- Synergy

- Properties suggested exploration of extended interval dosing

Pharmacodynamics of AMGs[2]

- Two predictors of efficacy
  - AUC_{24}:MIC
  - C_{max}:MIC
- AUC_{24}:MIC
  - Affected by V_d and Clearance
- C_{max}:MIC
  - Affected by V_d

Dosing Strategies[1]

- Traditional
  - Weight based dose divided 2-3 times daily in patients with normal renal function
  - The interval was extended to daily in impaired renal function
  - Use IBW (AdjBW if TBW ≥20% IBW)[3]

- Extended Interval
  - Higher weight based dose given daily or longer if patient has poor renal function
  - Use AdjBW (unless TBW is ≤IBW)[3]

Evidence for Extended Interval Dosing[2]

- Data shows superiority or equivalence for:
  - Clinical efficacy
  - Bacteriologic efficacy
  - Nephrotoxicity
  - Cost-effectiveness[1,3]

- No difference show for:
  - Auditory toxicity
  - Vestibular toxicity
  - Mortality rates

When to use Traditional Dosing?

- Burns (>20% body)[4]
- Pregnancy[4]
- Decreased renal function (<40 ml/min)[4]
- Dialysis[4]
- Ascites[4]
- Cystic Fibrosis[3]
- History of hearing loss[3]
- Gram positive infxns[3]
- Mycobacterial infxns[3]

AMG Extended Interval Dosing

- Gentamicin/Tobramycin
  - UTI – 3 mg/kg
  - Most infxns – 5 mg/kg
  - Life-threatening illness – 7 mg/kg
- Amikacin
  - 15-20 mg/kg
  - Last line for resistant organisms
  - Memorial – levels must be sent out for analysis

AMG Traditional Dosing

- Gentamicin/Tobramycin: 1-2 mg/kg/dose
- Amikacin: 5-7.5 mg/kg/dose

CrCl > 60	**Q 8 hrs**
CrCl 40-60	**Q 12 hrs**
CrCl 20-40	**Q 24 hrs**
CrCl < 20	**LD, monitor levels**

HD Dosing of Aminoglycosides[3]

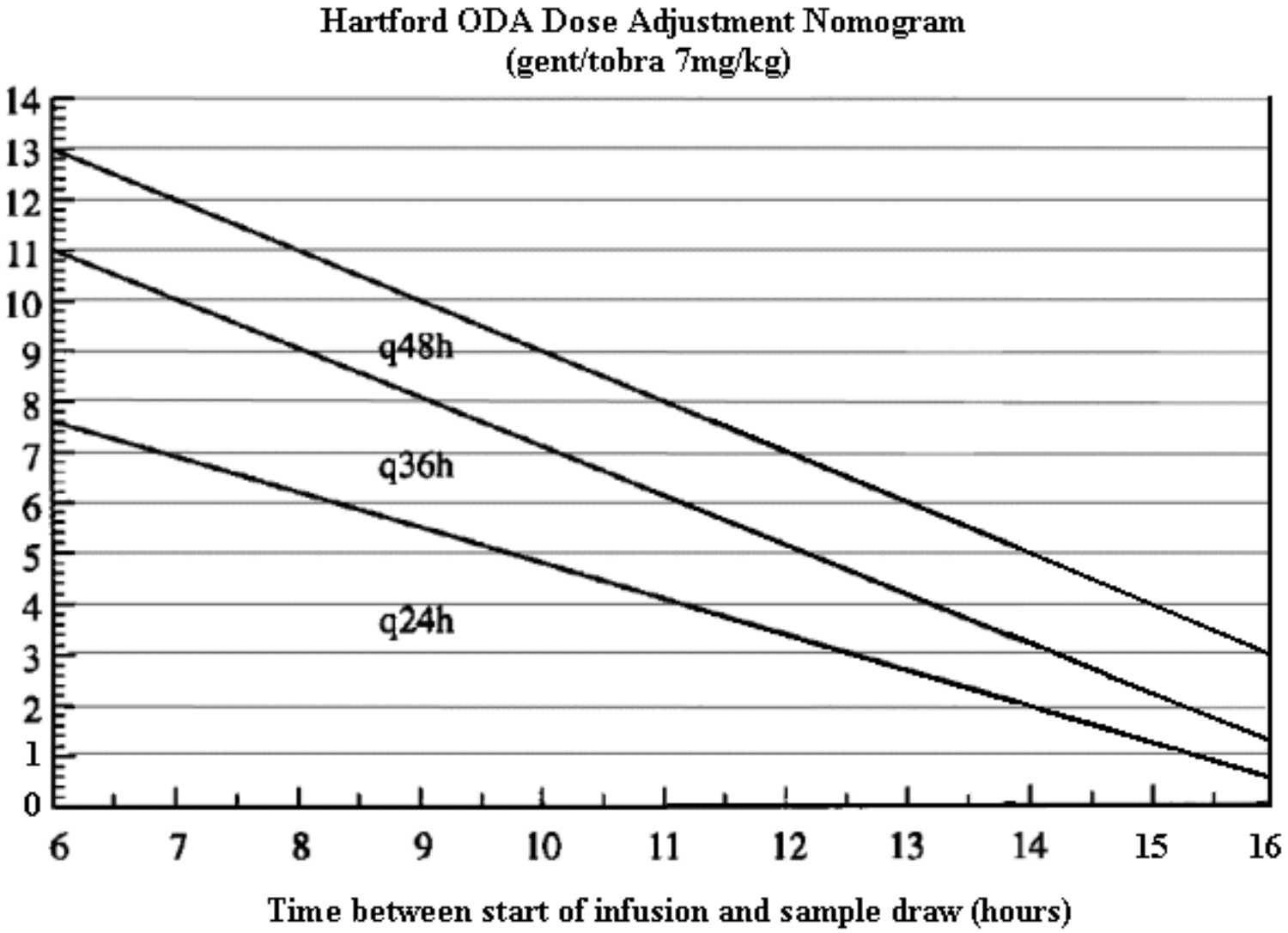
- Gentamicin/Tobramycin – Give after HD
  - Loading Dose: 2-3 mg/kg
  - Maintenance Dose:
    - Mild UTI or synergy = 1 mg/kg
    - Moderate to severe UTI = 1 – 1.5 mg/kg
    - Systemic GNR infection = 1.5 – 2 mg/kg
- Use IBW (if TBW ≥20% IBW use AdjBW)

Synergy Dosing of Aminoglycosides[5]

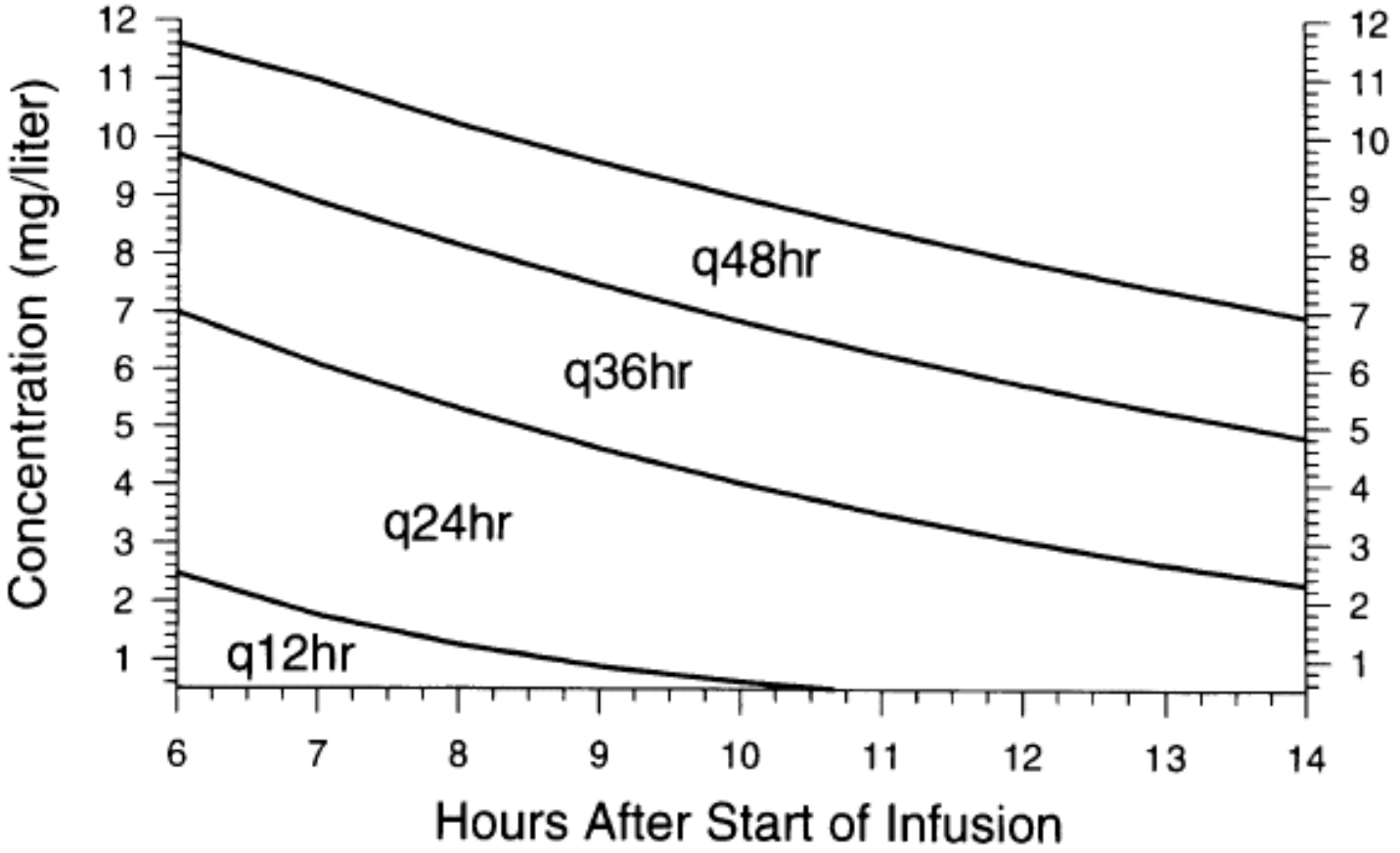
- When would synergy dosing be utilized?
- Dose of gentamicin = 1 mg/kg/dose Q8 hrs in patients with CrCl > 60 ml/min
- When should monitoring occur?
  - Patient on gentamicin ≥ 7 days
- Goal trough ≤ 1 mg/mL

How do we Monitor Extended Interval Dosing?

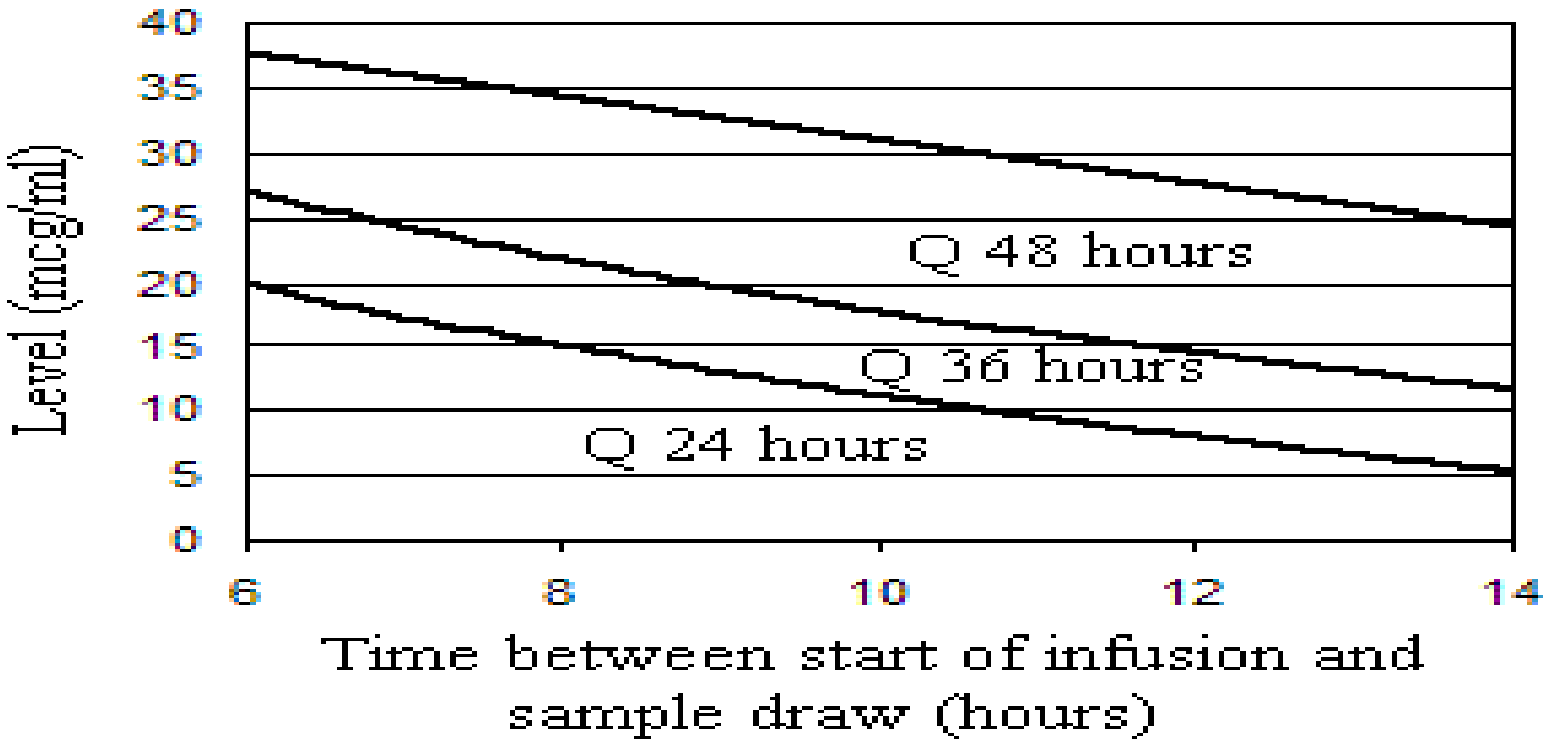
- Nomograms!
- After the first dose of Amikacin, Gentamicin or Tobramycin:
  - Draw random level 6-16 hours later and determine the appropriate frequency based on the nomograms provided in the AMG Reference


Hartford ODA Dose Adjustment Nomogram
(gent/tobra 7mg/kg)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
q48h
q36h
q24h
6
7
8
9
10
11
12
13
14
15
16
Time between start of infusion and sample draw (hours)

Gentamicin/Tobramycin 5 mg/kg dose[3]



Amikacin Extended Interval Dosing Nomogram (15mg/kg)



Monitoring Extended Interval Steady State Troughs[3]

Gentamicin/Tobramycin Trough Concentration	Amikacin Trough Concentration	Dosing Recommendation
< 1 mcg/mL	< 4 mcg/mL	Continue current dosing
1-3 mcg/mL	4-8 mcg/mL	Extend interval to 48 hours
> 3 mcg/mL	> 8 mcg/mL	Use traditional dosing

- For a true trough – draw level 30 min prior to next dose

Monitoring AMGs During Traditional Dosing

- Use peaks and troughs
- Peaks – drawn 30 minutes after end of infusion
- Troughs – drawn right before next dose

Drug	Peak (mcg/mL)	Trough (mcg/mL)
Gentamicin/Tobramycin	5-10	< 2
Amikacin	20-30	< 5

Monitoring AMGs During HD Dosing

- Draw pre-HD levels
- Re-dose based the following levels:

LEVELS	DOSES
< 1 mg/L	1 mg/kg after HD
< 1.5-2 mg/L	1-1.5 mg/kg after HD
< 2 mg/L	1.5-2 mg/kg after HD

Why do we monitor AMG levels?[1,2]

- Toxicity
  - Nephrotoxicity - reversible
  - Ototoxicity - irreversible
  - Neuromuscular Blockade

Questions??

References

1. Drew RH. Aminoglycosides. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 8, 2014.)
2. Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin N Am* 17(2003) 503-528.
3. Aminoglycoside Reference. Memorial Health Care System. Accessed August 8, 2014.
4. Drew RH. Dosing and administration of parenteral aminoglycosides. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on August 8, 2014.)
5. University of California San Francisco. Aminoglycoside Dosing and Monitoring. Accessed August 10, 2014. http://clinicalpharmacy.ucsf.edu/idmp/adult_guide/aminoglycoside_dosing.htm.