Therapeutic Drug Monitoring

AMINOGLYCOSIDE

Introduction

- The *aminoglycoside antibiotics* are bactericidal agents that are widely used for the treatment of gram-negative infections such as pneumonia or bacteremia, often in combination with a β-lactam antibiotic.
- Aminoglycosides are also used for gram-positive infections such as infective endocarditis in combination with penicillins when antibiotic synergy is required for optimal killing.

Introduction

- Aminoglycosides exhibit
  - *concentration-dependent bacterial killing* that kill bacteria at a faster rate when drug concentrations are higher.
  - *concentration-dependent postantibiotic effect*. The bacterial killing continues even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).
- Because the postantibiotic effect is concentration-dependent for the aminoglycosides , higher drug concentrations lead to a longer postantibiotic effect.

Conventional Dosing

- Aminoglycoside antibiotics are given as short-term (1/2–1 hour) infusions.
- If a 1-hour infusion is used, peak concentrations are measured when the infusion is completed.
- If a 1/2-hour infusion is used, serum concentrations exhibit a distribution phase so that drug in the blood and in the tissues are not yet in equilibrium. Because of this, a 1/2-hour waiting period is allowed for distribution to finish before peak concentrations are measured.

Conventional Dosing

- In general, therapeutic *steady-state peak concentrations* for gentamicin, tobramycin, and netilmicin are *5–10 μg/mL* for gram-negative infections.

- Infection sites with more susceptible bacteria, such as intraabdominal infections usually can be treated with steady-state peak concentrations at the lower end of this range (typically 5–7 μg/mL).

Conventional Dosing

- Infection sites that are difficult to penetrate and with bacteria that have higher MIC values, such as pseudomonal pneumonia usually require steady-state peak concentrations in the higher end of the range (typically 8–10 μg/mL).

- When gentamicin, tobramycin, or netilmicin are used synergistically with penicillins or other antibiotics for the treatment of gram-positive infections such as infective endocarditis , steady-state peak concentrations of 3–5 μg/mL are often times adequate.

Conventional Dosing

- Therapeutic peak concentrations for amikacin are 15–30 μg/mL.
- Exceeding peak steady-state concentrations of 12–14 μg/mL for gentamicin, tobramycin, or netilmicin or 35–40 μg/mL for amikacin when using conventional dosing leads to an increased risk of ototoxicity.

Conventional Dosing

- Trough steady-state concentrations (predose or minimum concentrations usually obtained within 30 minutes of the next dose) above 2–3 μg/mL for tobramycin, gentamicin, or netilmicin or 10 μg/mL for amikacin predispose patients to an increased risk of nephrotoxicity

Conventional Dosing

Keeping in mind

- Peak and trough concentrations within the suggested ranges does not completely avoid nephrotoxicity and ototoxicity in patients, but, hopefully, decreases the likelihood that patients will experience these serious adverse effects.

Conventional Dosing

Besides to therapeutic range,

- duration of therapy (exceeding 14 days)
- large total cumulative doses
- concurrent therapy with other nephrotoxic drugs such as vancomycin

➢ ***can predispose patients to these side effects of the aminoglycoside antibiotics***

Extended-Interval Dosing

- Because aminoglycoside exhibit concentration-dependent bacterial killing and the postantibiotic effect that increase with high concentration, investigators began studying the possibility of giving a higher dose of aminoglycoside once daily.

- Clinicians have begun using extended-interval dosing in selected patients.

Extended-Interval Dosing

- Because of the extremely high peak concentrations obtained during extended-interval dosing of aminoglycosides, it can be difficult to understand why increased toxicity is not seen in patients.
- The hypothesized reason is that both nephrotoxicity and ototoxicity are due to accumulation of aminoglycoside in the relevant tissue.

Extended-Interval Dosing

- Because the dosage interval is prolonged in extended-interval administration, aminoglycoside concentrations are low for a long period of time and may allow for diffusion of drug out of tissue and into the blood which avoids drug accumulation in the ear and kidney.
- Possible side effects:
  - infusion-related hypotension
  - Acute neuromuscular blockade, usually associated with concurrent administration of anesthetics

Extended-Interval Dosing

Estimated CrCl (mL/min)	Initial Dosing Interval
> 60 mL/min	Q24H
40-59 mL/min	Q36H
20-39 mL/min	Q48H
< 20 mL/min	Not recommended

Dosing Summary

- Extended interval aminoglycoside dosing (EIAD)is preferred over traditional dosing. EIAD typically employs a daily dose of 7 mg/kg (5 mg/kg/day for UTI is reasonable) and is usually dosed q24h in patients with normal renal function. This approach is designed to produce higher peak concentrations than seen with conventional dosing .

- The use of the 24-hour dosing interval is designed to create an "aminoglycoside-free" period during the dosage interval. This period will reduce accumulation of aminoglycosides in tissues and result in less net transfer of aminoglycoside from the blood into the tissue.
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Dosing Summary

- Uptake of aminoglycosides by tissues (e.g. nephron) is a saturable process. Smaller but more frequent doses are not believed to saturate drug transport into the tissue and ultimately produce higher tissue concentrations than EIAD.

- An "aminoglycoside-free" period also assist in preventing the development of adaptive resistance to aminoglycosides antibiotics.

Clinical Monitoring Parameters

- Serial monitoring of serum creatinine concentrations should be used to detect nephrotoxicity.
- Ideally, a baseline serum creatinine concentration is obtained before aminoglycoside therapy is initiated and three times weekly during treatment.
- An increasing serum creatinine test on two or more consecutive measurement occasions indicates that more intensive monitoring of serum creatinine values, such as daily, is needed.

Clinical Monitoring Parameters

- In the clinical setting, audiometry is rarely used to detect ototoxicity. Instead, clinical signs and symptoms of auditory or vestibular ototoxicity are monitored at the same time intervals as serum creatinine determination.

Basic Clinical Pharmacokinetic Parameters

- The aminoglycosides are eliminated almost completely (≥90%) unchanged in the urine primarily by glomerular filtration.
- These antibiotics are usually given by short-term intermittent intravenous infusions, although they can be given intramuscularly.
- When given intramuscularly they exhibit very good bioavailability of ~100% and are rapidly absorbed with maximal concentrations occurring about 1 hour after injection.

Basic Clinical Pharmacokinetic Parameters

- *Exceptions to this situation are patients who are*
  - hypotensive
  - obese
- Oral bioavailability is poor (<10%) so systemic infections cannot be treated by this route of administration.
- Plasma protein binding is low (<10%).
- The half life of aminoglycosides is ~2-3 hours with normal renal function

Basic Clinical Pharmacokinetic Parameters

- Recommended doses for conventional dosing in patients with normal renal function are

3–5 mg/kg/d for gentamicin and tobramycin

4–6 mg/kg/d for netilmicin

15 mg/kg/d for amikacin

- These amounts are divided into three equal daily doses for gentamicin, tobramycin, or netilmicin, or two or three equal daily doses for amikacin.

Basic Clinical Pharmacokinetic Parameters

- Extended-interval doses for patients with normal renal function are

4–7 mg/kg/d for

gentamicin , tobramycin and netilmicin

11–20 mg/kg/d for amikacin

Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing

- Severe renal disease (creatinine clearance [CrCl] <30 mL/min)
- Dialysis
- Cystic fibrosis
- Geriatric and pediatric
- Ascites/severe liver disease
- Cirrhosis
- Extensive burns (>40% of total body SA)

Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing

- The elimination rate constant (ke) for aminoglycoside antibiotics increases in proportion with creatinine clearance (CrCl).
- The equation for this relationship is

$$ke\ (\text{in } h^{-1}) = 0.00293(\text{CrCl in mL/min}) + 0.014$$

Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing

- A major body burn (>40% body surface area) can cause large changes in aminoglycoside pharmacokinetics.
- Forty-eight to seventy-two hours after a major burn, the basal metabolic rate of the patient increases to facilitate tissue repair.
- Because of the increase in basal metabolic rate, glomerular filtration rate increases which increases aminoglycoside clearance.

Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing

- Generally cystic fibrosis patients have decreased adipose tissue and increased extracellular fluid due to disease-state. So it has larger volume of distribution.

- These patients also have higher aminoglycoside clearance values due to increased glomerular filtration rates.

Effects of Disease States and Conditions on Aminoglycoside Pharmacokinetics and Dosing

- Paediatric patients have a larger amount of body water compared to adults.
- Aminoglycoside volume of distribution is larger (0.3–0.6 L/kg).
- Additionally, kidneys are not completely developed, so glomerular filtration and aminoglycoside clearance are decreased.
- At that time, aminoglycoside volume of distribution, clearance, and half-life gradually approach adult values at puberty (~12–14 years old).

Drug Interactions

- Vancomycin, amphotericin B, cyclosporin, and furosemide enhance the nephrotoxicity potential of the aminoglycosides.

- Loop diuretics including furosemide and bumetanide can increase the incidence of ototoxicity when aminoglycosides have been coadministered.

Drug Interactions

- Penicillins (primarily penicillin G, ampicillin, nafcillin, carbenicillin, ticarcillin) can inactivate aminoglycosides in vivo and in blood specimen tubes intended for the measurement of aminoglycoside serum concentrations.

- These two classes of drugs can also inactive each other in intravenous administration bags and syringes and should not be mixed together.

Initial Dosage Determination

- **Pharmacokinetic Dosing Method**

1. *Elimination rate constant estimate*
2. *Volume of distribution estimate*
3. *Selection of appropriate pharmacokinetic equations*
4. *Steady-state concentration selection*
5. *Dosage computation*

Example 1

- DQ is a 20-year-old, 61-kg (height = 5 ft 8 in) male with a pulmonary exacerbation due to cystic fibrosis. His current serum creatinine is 0.7 mg/dL and is stable. Compute a tobramycin dose for this patient using extended-interval dosing.

Answer

1. ***Estimate creatinine clearance***

$$\text{CrCl}_{est} = [(140 - \text{age})\text{BW}] / (72 \cdot \text{SCr})$$
$$= [(140 - 20\ \text{y})61\ \text{kg}] / (72 \cdot 0.7\ \text{mg/dL})$$
$$\text{CrCl}_{est} = 145\ \text{mL/min}$$

2. *Estimate elimination rate constant and half-life.*

$ke = 0.00293(CrCl) + 0.014$

$= 0.00293(145\ mL/min) + 0.014$

$= 0.439\ h^{-1}$

$t1/2 = 0.693 / ke$

$= 0.693 / 0.439\ h{-}1 \quad = 1.6\ h$

3. *Estimate volume of distribution (V).*

The patient has cystic fibrosis, so the volume of distribution equals 0.35 L/kg:

$V = 0.35\ L/kg\ (61\ kg)$

$= 21.4\ L$

4. ***Choose desired steady-state serum concentrations.***

Cssmax = 30 μg/mL and Cssmin = 0.01 μg/mL.

5. ***Use intermittent intravenous infusion equations to compute dose***

$\tau = [(\ln Cssmax - \ln Cssmin) / ke] + t'$

$= [(\ln 30\ \mu g/mL - \ln 0.01\ \mu g/mL) / 0.439\ h^{-1}] + 1\ h$

$= 19.2\ h$ round to 24 hr

$$k0 = Css_{max}\, keV[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$$

$$k0 = (30\ mg/L \cdot 0.439\ h^{-1} \cdot 21.4\ L)\{[1 - e^{-(0.439\ h^{-1})(24\ h)}] / [1 - e^{-(0.439\ h^{-1})(1\ h)}]\}$$

$$= 793\ mg$$

The prescribed maintenance dose would be 800 mg every 24 hours.

$$LD = k0 / (1 - e^{-k\tau})$$

$$= 800\ mg / (1 - e^{-(0.439\ h^{-1})(24\ h)})$$

$$= 800\ mg$$

Example 2

PQ is a 75-year-old, 62-kg (5 ft 9 in) male with gram-negative sepsis. His current serum creatinine is 1.3 mg/dL, and it has been stable since admission. Compute a gentamicin dose for this patient to provide a steady-state peak concentration of 8 μg/mL and a steady-state trough concentration of 1.5 μg/mL using conventional dosing.

1. ***Estimate creatinine clearance.***

$$CrCl_{est} = [(140 - age)BW] / (72 \cdot SCr)$$

$$= [(140 - 75\ y)62\ kg] / (72 \cdot 1.3\ mg/dL)$$

$$CrCl_{est} = 43\ mL/min$$

2. ***Estimate elimination rate constant and half-life.***

$$k_e = 0.00293(CrCl) + 0.014$$

$$= 0.00293(43\ mL/min) + 0.014$$

$$= 0.140\ h^{-1}$$

$$t_{1/2} = 0.693 / k_e$$

$$= 0.693 / 0.140\ h^{-1}$$

$$= 4.9\ h$$

3. *Estimate volume of distribution (V).*

The patient has no disease states or conditions that would alter the volume of distribution from the normal value of 0.26 L/kg:

V = 0.26 L/kg (62 kg) = 16.1 L

4. *Choose desired steady-state serum concentrations.*

- Gram-negative sepsis patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Cssmax) equal to 8–10 μg/mL; steady-state trough (Cssmin) concentrations should be <2 μg/mL to avoid toxicity.
- Set Css_{max} = 8 μg/mL and Css_{min} = 1.5 μg/mL.

5. ***Use intermittent intravenous infusion equations to compute dose.***

$$\tau = [(\ln C_{ssmax} - \ln C_{ssmin})/k_e] + t'$$

$$= [(\ln 8\ \mu g/mL - \ln 1.5\ \mu g/mL) / 0.140\ h^{-1}] + 1\ h$$

$$= 12.9\ h$$

$$k0 = Css_{max} keV[(1 - e^{-ke\tau}) / (1 - e^{-ket'})]$$

$$k0 = (8\ mg/L \cdot 0.140\ h{-}1 \cdot 16.1\ L)\{[1 - e^{-(0.140\ h\ -1)(12\ h)}] / [1 - e^{-(0.140\ h{-}1)(1\ h)}]\}$$

$$= 112\ mg$$

The prescribed maintenance dose would be 110 mg every 12 hours.

6. ***Compute loading dose (LD), if needed.***

$$LD = k0 / (1 - e^{-ke\tau})$$

$$= 110\ mg / [1 - e^{-(0.140\ h{-}1)(12\ h)}]$$

$$= 135\ mg$$

Hartford Nomogram Method for Extended-Interval Dosing

Therapeutic monitoring and dose adjustment

Levels should be obtained only in the following situations:

- Random serum level 6-14 hours **AFTER THE START** of the infusion of the first dose to confirm appropriate serum level.
- Confirm an appropriate serum concentration after dosage adjustment.
- Suspected toxicity (oto- or nephro-) or when there is a change in or impaired renal function while on maintenance therapy.
- Weekly monitoring of prolonged therapy with aminoglycosides

- **Dosage adjustments should be made according to the Hartford Nomogram**

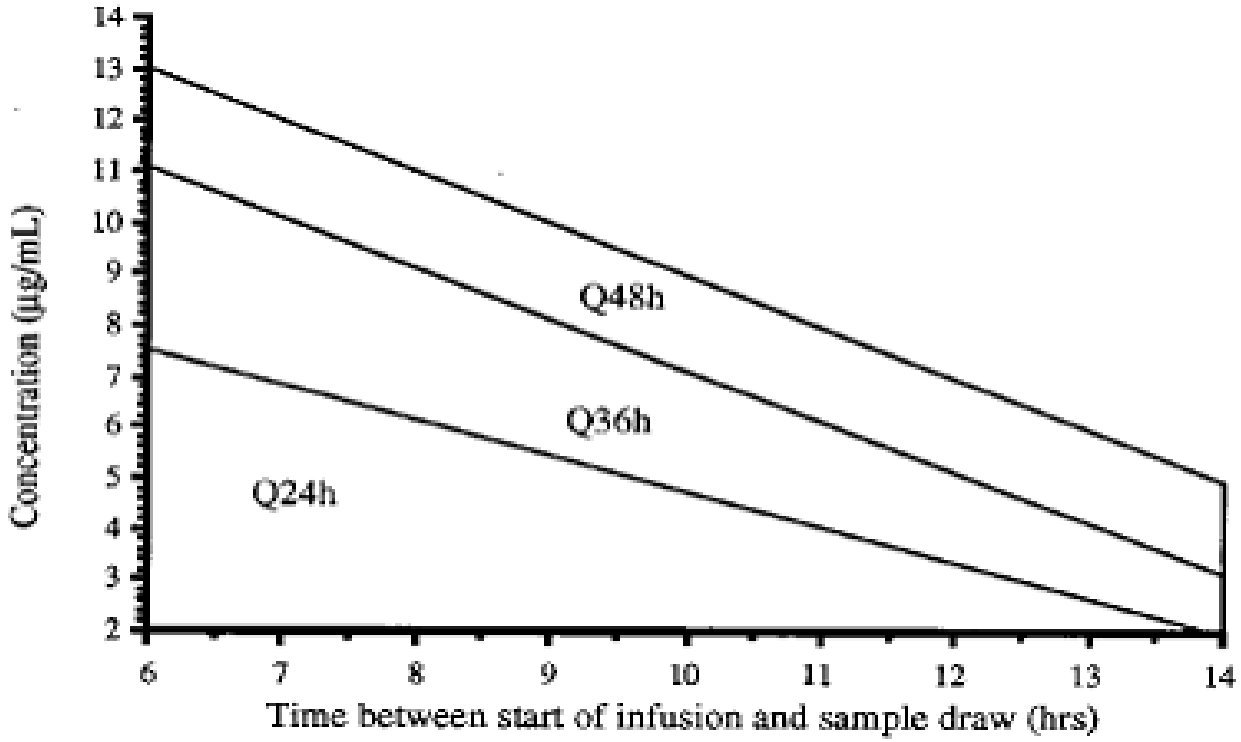

FIG. 1. ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

Important Notes:

- Because the Hartford Nomogram was based on a dose of 7mg/kg, if a lower dose is being used, the resultant level should be multiplied by a factor equal to 7 mg divided by the dose used.

- Example: If a patient is receiving 5mg/kg/day and the 10h post-dose level was 2 mcg/mL, you would multiply the level by 1.4 (7/5) to give a level of 2.8 mcg/mL. This adjusted level is the one you would plot on the Hartford Nomogram.

- If using amikacin, plot ½ of the serum concentration on the nomogram.

- If the level falls on the line, choose the longer interval for administration.

- If the aminoglycoside level falls off the nomogram, traditional dosing should be used.

Use of Aminoglycoside Serum Concentrations to Alter Dosages Example 3

Patient was prescribed gentamicin 110 mg every 12 hours. Steady-state gentamicin concentrations were obtained before and after the fourth dose, and the peak concentration (obtained 1/2 hour after a 1/2-hour infusion of gentamicin) was 9.5 μg/mL while the trough concentration (obtained within 1/2 hour before dosage administration) was 3.0 μg/mL. Compute a revised gentamicin dose for this patient to provide a steady-state peak concentration of 8 μg/mL and a steady-state trough concentration of 1 μg/mL using conventional dosing.

Example 3

- ***Compute the patient's elimination rate constant and half-life.*** *(Note: For infusion times less than 1 hour, t' is considered to be the sum of the infusion and waiting times.)*

$$ke = (\ln Cssmax - \ln Cssmin) / \tau - t'$$

$$= (\ln 9.5\ \mu g/mL - \ln 3\ \mu g/mL) / (12\ h - 1\ h)$$

$$= 0.105\ h^{-1}$$

$$t1/2 = 0.693 / ke$$

$$= 0.693 / 0.105\ h^{-1} = 6.6\ h$$

Example 3

- ***Compute the patient's volume of distribution.***

$$V = [k_0 (1 - e^{-ke\ t'})]/\{k_e [C_{max} - (C_{predose}\ e^{-ke\ t'})]\}$$

$$= (110\ mg/1\ h)[1 - e^{-0.105\ h)(1\ h)}]/0.105\ h^{-1}\{9.5\ mg/L - [3\ mg/L\ e^{-(0.105\ h^{-1})(1\ h)}]\}$$

$$V = 15.4\ L$$

Example 3

- ***Determine the new dosage interval for the desired concentrations***

$\tau = [(\ln Css_{max} - \ln Css_{min}) / ke] + t'$

$= [(\ln 8\ \mu g/mL - \ln 1\ \mu g/mL) / 0.105\ h^{-1}] + 1\ h$

$= 21\ h$, round to 24 h

Example 3

- ***Determine the new dose for the desired concentrations***

$$k0 = Css_{max}\, keV[(1 - e^{-ke\tau}) / (1 - e^{-ket'})]$$

$$k0 = (8\ mg/L \cdot 0.105\ h{-}1 \cdot 15.4\ L)\{[1 - e^{-(0.105\ h-1)(24\ h)}] / [1 - e^{-(0.105\ h-1)(1\ h)}]\}$$

$$= 119\ mg, \text{ rounded to } 120\ mg$$

- A dose of gentamicin 120 mg every 24 hours would be prescribed to begin 24 hours after the last dose of the previous regimen.

Linear Pharmacokinetics Method

- Because aminoglycoside antibiotics follow linear, dose-proportional pharmacokinetics, steady-state serum concentrations change in proportion to dose according to the following equation:
- **Dnew/ Css,new = D old / Css,old or**
- **Dnew= (Css,new/ Css,old). D old**
- where **D** is the dose, **Css** is the steady-state peak or trough concentration, old indicates the dose that produced the steady-state concentration that the patient is currently receiving, and new denotes the dose necessary to produce the desired steady-state concentration.

Example 4

- **JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia.** His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 170 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 9 μg/mL and 1 μg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 μg/mL and 1.4 μg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 μg/mL.
- D new = 0.75 * 170 = 135 mg