Aminoglycosides

Uses: Treatment of serious **gram-negative systemic infections** and some **gram-positive infections** such as infective endocarditis.

Disadvantage: aminoglycosides are their association with **nephrotoxicity** and **ototoxicity**, both of which are associated with **elevated trough levels** and **sustained elevated peak levels.**

Characteristics:

-**Bactericidal**

-**Concentration dependent bacterial killing** (faster killing with increase dose)

-**Concentration-dependent postantibiotic effect**. [continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).]

Method of Dosing:

-Conventional dosing (**multiple dose administration per day) (usually TID)**

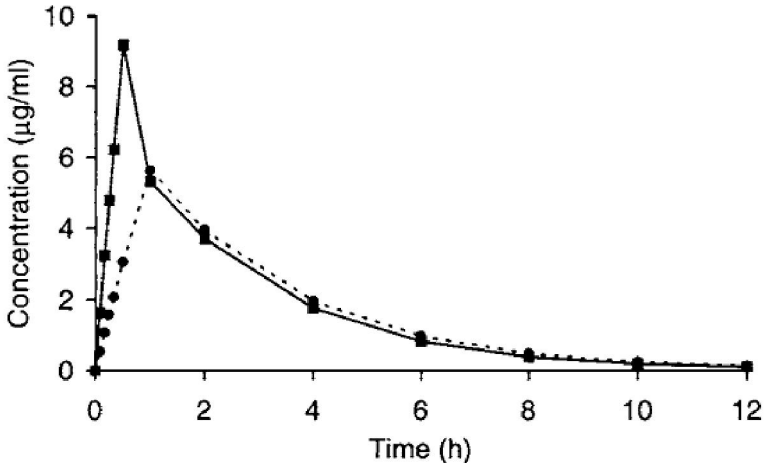
- Extended interval **(usually the total daily dose given once per day)**

How to administrate

-IM

-IV as short-term (1/2–1 hour) infusions

- **If infusion time = 1hr** plasma concentration at the end of infusion represents **Cssmax** and **Plasma conc.= tissue conc.**
- **If infusion time = 0.5hr** plasma concentration at the end of infusion represents **Plasma conc.> tissue conc.**



Aminoglycosides concentration toxicity relationship

-**Nephrotoxicity** appear **after 3–5 days** of therapy with proper dosing of the antibiotic -trough conc. above **2–3 µg/mL for tobramycin, gentamicin, or netilmicin** or **10 µg/mL for amikacin** predispose patients to an increased risk of nephrotoxicity.

- aminoglycoside-induced nephrotoxicity is usually reversible

Ototoxicity (irreversible damage), 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.

BASIC CLINICAL PHARMACOKINETIC PARAMETERS

Absorption

- Oral F (poor, 0.3-1.5%)
- IM/IV F 100%
- IM Tpeak approx 1 hour (0.5-2.0 hrs) Avoid in critically ill patients
- IM malabsorbed in hypotensive patients, such as those with gram-negative sepsis.
- „ S = 1

Non Obese adults with normal renal function (creatinine clearance >80 mL/min,) have

-$T_{0.5}$ = 2 hours (range: 1.5–3 hours),

- Vd = 0.26 L/kg (range: 0.2–0.3 L/kg).

- Cl = GFR = CrCl (Creatinine Clearance)

Distribution

-Distributed to extracellular water 0.20 – 0.26 L/kg

-Significant accumulation in kidney cortex, and inner ear

- Distributes well to: Ascitic, pericardial, peritoneal, pleural, synovial fluids

-Crosses placenta Fetal concentrations are 16-50% of maternal Concentrations

-Poor distribution into CSF and vitreous humor

Volume of Distribution	Range (L/kg)	Average (L/kg)
Adult	0.07- 0.7	0.26
children	0.07- 0.7	0.45
neonate	0.2 -0.6	Variable (under AGE)

Protein Binding 0-30%

Factors Affecting Distribution

Volume of Distribution	Average (L/kg)
-Increased VD	
Obesity	VD = 0.26 L/kg [IBW + 0.4 (TBW – IBW)] Morbidly obese patients (BMI>35%) VD = 0.18 L/kg TBW
Ascites	VD = (0.26 L/kg * Wt $_{NO\ ascites}$)+ (1 L/kg * Ascites Volume)
Cystic fibrosis	0.35L/Kg
Pregnancy/postpartum	Poor data
Edema	Like ascites
Age	
Premature infants (gestational age ≤34wks)	(0.5–0.6 L/kg)
Full-term neonates (gestational age ~40weeks)	(mean V = 0.4–0.5 L/kg)
6 months to <2 years	(V = 0.3–0.4 L/kg)
≥2 years	Adult value 0.26 L/kg)
-Decrease VD	
Dehydration	

Elimination

Route: Almost totally excreted unchanged in **urine via glomerular filtration**

Washing out period: Complete recovery of a **single dose** in **urine takes 10-20 days** with **normal renal function** due to slow release from deep tissue compartment.

Factors affect Clearance

Clearance	Average T0.5
-Decreased	
renal failure	50 hours (range: 36–72 hours)
Peritoneal dialysis	36hr
AGE	
Premature infants (gestational age ≤34wks)	6–10 hours (premature kidneys)
Full-term neonates (gestational age ~40weeks)	(t1/2 = 4–5 hours) (kidneys still not with fully function)
6 months to <2 years	(t1/2 = 2–3 hours) (kidneys fully function)
-Increase	

Morbid Obese	**variable**
Burn	**1.5 hours**
Cystic fibrosis	**1.5 hours (Variable t1/2 during therapy)**
Pregnancy/postpartum	**Varies „ (Returns to baseline post-partum)**

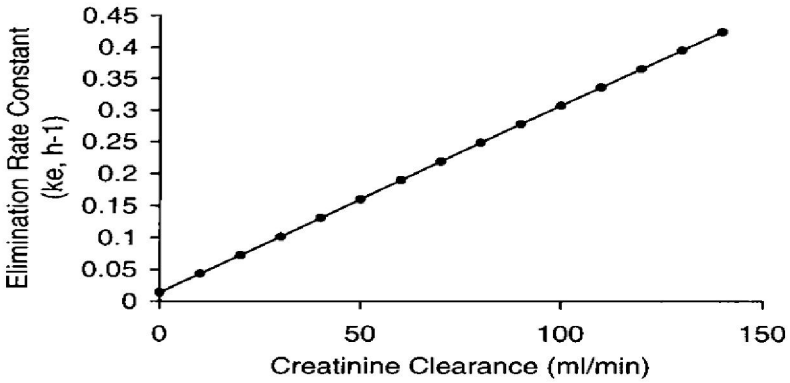


FIGURE 4-2 Relationship between renal and aminoglycoside elimination. The elimination rate constant (k_e) for aminoglycoside antibiotics increases in proportion with creatinine clearance (CrCl). The equation for this relationship is k_e (in h^{-1}) = 0.00293(CrCl in mL/min) + 0.014. This equation is used to estimate the aminoglycoside elimination rate constant in patients for initial dosing purposes.

Recommended doses

- Conventional dosing in adult patients with normal renal function

gentamicin and tobramycin	**3–5 mg/kg/d**	**TID**
netilmicin	**4–6 mg/kg/d**	**TID**
amikacin	**15 mg/kg/d**	**BID or TID**

-Extended-interval doses (adult+normal renal function)

gentamicin and tobramycin	**4–7 mg/kg/d**
netilmicin	**4–7 mg/kg/d**
amikacin	**11–20 mg/kg/d**

AMINOGLYCOSIDE	ROUTE	AGE 0–4 WEEK OLD	AGE <1 WEEK OLD		AGE ≥ 1 WEEK OLD	
		WEIGHT <1200 g	WEIGHT 1200–2000 g	WEIGHT >2000 g	WEIGHT 1200–2000 g	WEIGHT >2000 g
Amikacin	IV, IM	7.5 mg/kg every 18–24 hours	7.5 mg/kg every 12 hours	7.5–10 mg/kg every 12 hours	7.5–10 mg/kg every 8 or 12 hours	10 mg/kg every 8 hours
Gentamicin or Tobramycin	IV, IM	2.5 mg/kg every 18–24 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 8 or 12 hours	2.5 mg/kg every 8 hours

****Extended-interval aminoglycoside dosing can be conducted in pediatric patients**

INITIAL DOSAGE DETERMINATION METHODS

1. Pharmacokinetic Dosing Method

❶ ELIMINATION RATE CONSTANT ESTIMATE

Use this equation **ke =0.00293(CrCl)(ml/min) + 0.014**

-Crcl estimated from Cockroft & Gault equation for non obese

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

Crcl multiply By **1 for male** and **0.85 for female**

or Salazar eq. for obese

- M: IBW (kg) = 50 kg + 2.3 (Ht. Inches > 5')
- F: IBW (kg) = 45.4 kg + 2.3 (Ht. Inches >

Weight Considerations

„ Wt = IBW for non-obese patients

„ Wt = Actual body weight if patient weighs less than IBW

„ -Use Adjusted Body Weight for obese patients*

„ -Definitions

„ **Obese:** TBW greater that 1.2 x IBW

„ **Morbidly Obese:** TBW equal or greater than 2 x IBW

„ Wt for CrCl in obese patients **= IBW + 0.4(TBW – IBW)**

❷ VOLUME OF DISTRIBUTION ESTIMATE

According to the values in the table

❸ STEADY-STATE CONCENTRATION SELECTION

infection	Peak Cp (mcg/ml=mg/L)	Trough Cp (mcg/ml=mg/L)
	Amikacin, Kanamycin	
Less severe Soft tissue	15 – 25	1 – 4
Severe, Sepsis, pneumonia Burn pt, Immunosuppressed	25 – 30	4 - 8
	gentamicin, tobramycin & netilmicin	
Less severe Soft tissue	5–7	1.5-2
Severe, Sepsis, pneumonia Burn pt, Immunosuppressed	8–10 µg/mL	≤2

❹ Determine Need for Loading Dose (LD)

TABLE 4-2A One-Compartment Model Equations Used with Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$C = (D/V)e^{-k_e t}$	$C = (D/V)e^{-k_e t}[(1 - e^{-nk_e \tau}) / (1 - e^{-k_e \tau})]$	$C = (D/V)[e^{-k_e t} / (1 - e^{-k_e \tau})]$
Intermittent intravenous infusion	$C = [k_0 / (k_e V)](1 - e^{-k_e t'})$	$C = [k_0 / (k_e V)](1 - e^{-k_e t'}) \cdot [(1 - e^{-nk_e \tau}) / (1 - e^{-k_e \tau})]$	$C = [k_0 / (k_e V)][(1 - e^{-k_e t'}) / (1 - e^{-k_e \tau})]$

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, k_e is the elimination rate constant, n is the number of administered doses, τ is the dosage interval, t′ is the infusion time, k_0 is the infusion rate. Maximum steady-state concentrations are denoted as $Cmax_{ss}$, Css_{max}, or Cmax,ss. Minimum steady-state concentrations are denoted as $Cmin_{ss}$, Css_{min}, or Cmin,ss.

TABLE 4-2B Pharmacokinetic Constant Computations Utilizing a One-Compartment Model for Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	SINGLE DOSE	MULTIPLE DOSE	STEADY STATE
Intravenous bolus	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D/C_0$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D / (C_0 - C_{predose})$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = D / (C_0 - C_{predose})$ $Cl = k_e V$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$	$k_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$ $t_{1/2} = 0.693 / k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose} e^{-k_e t'})]\}$ $Cl = k_e V$

Symbol key: C_1 is drug serum concentration at time = t_1, C_2 is drug serum concentration at time = t_2, k_e is the elimination rate constant, $t_{1/2}$ is the half-life, V is the volume of distribution, k_0 is the continuous infusion rate, t′ is the infusion time, D is dose, C_0 is the concentration at time = 0, Cl is drug clearance, $C_{predose}$ is the predose concentration.

TABLE 4-2C Equations Used to Compute Individualized Dosage Regimens for Various Routes of Administration Used with Aminoglycoside Antibiotics

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D OR K_0), AND LOADING DOSE (LD) EQUATIONS
Intravenous bolus	$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e$ $D = Css_{max} V(1 - e^{-k_e\tau})$ $LD = Css_{max} V$
Intermittent intravenous infusion	$\tau = [(\ln Css_{max} - \ln Css_{min}) / k_e] + t'$ $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau}) / (1 - e^{-k_e t'})]$ $LD = k_0 / (1 - e^{-k_e\tau})$

Symbol key: Css_{max} and Css_{min} are the maximum and minimum steady-state concentrations, k_e is the elimination rate constant, V is the volume of distribution, k_0 is the continuous infusion rate, t' is the infusion time.

Example 1 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. **Compute a gentamicin dose for this patient using conventional dosing.**

1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is not obese. The Cockcroft-Gault equaion can be used to estimate creatinine clearance:

CrCl= [(140 – age)BW] / (72 · SCr) = [(140 – 50 y)70 kg] / (72 · 0.9 mg/dL)

CrCl= 97 mL/min.

2. Estimate elimination rate constant (ke) and half-life (t1/2).

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

ke = 0.00293(CrCl) + 0.014 = 0.00293(97 mL/min) + 0.014 = **0.298 h–1**

$t_{1/2}$ = 0.693/ke = 0.693/0.298 h–1 **= 2.3 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:**

Vd = 0.26 L/kg (70 kg) = **18.2 L**

4. Choose desired steady-state serum concentrations.

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations **(Cssmax) equal to 8–10 µg/mL**; steady-state trough **(Cssmin) <2 µg/mL** to avoid toxicity.

Set Cssmax = 9 µg/mL and Cssmin = 1 µg/mL.

5. Use intermittent intravenous infusion equations to compute dose

5.A. Calculate required dosage interval (τ) using a 1-hour infusion:

$\tau = [(\ln C_{ssmax} - \ln C_{ssmin}) / k_e] + t' = [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL) / 0.298\ h^{-1}] + 1\ h$ **τ= 8.4 h**

Note: Dosage intervals should be rounded to clinically acceptable intervals of 8 hours, 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter,

5.B. Calculate required dose rate or rate of infusion:

$k_0 = Css_{max} k_e Vd[(1 - e^{-ke.\tau}) / (1 - e^{-ke.t'})]$

$k_0 = (9\ mg/L \cdot 0.298\ h^{-1} \cdot 18.2\ L)\{[1 - e^{-(0.298\ h-1)(8\ h)}] / [1 - e^{-(0.298\ h-1)(1\ h)}]\} =$ **172 mg**

Note:

Fraction replacement $=(1 - e^{-ke.\tau})$

Fraction accumulation $=1/(1 - e^{-ke.t'})$

Aminoglycoside doses should be rounded to the nearest 5–10 mg. This dose would be rounded to 170 mg.

The prescribed maintenance dose would be 170 mg every 8 hours.

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

Note: if CrCL< 60 mL/min LD IS REUIRED

$LD = k0/(1 - e^{-ke.\tau}) = 170\ mg / [1 - e^{-(0.298\ h-1)(8\ h)}] = 187\ mg$

OR $LD = C_{MAX} .VD = 9mg/dl * 18.2 = 163.8mg \approx 164$ rounded to 170mg

Note: this loading dose ≈10% >or< M. Dose and **wouldn't be given to the patient.**

Example 2: ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intra-abdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient using conventional dosing.

1. Estimate creatinine clearance.

This patient has a stable serum creatinine and is **obese**

[$IBW_{females}$ (in kg) = 45 +2.3(Ht − 60 in) = 45 + 2.3(65 − 60) = 57 kg]. The Salazar and Corcoran equation can be used to estimate creatinine clearance:

Note: Height is converted from inches to meters: Ht = (65 in · 2.54 cm/in) / (100 cm/m) =1.65 m.

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

2. Estimate elimination rate constant (ke) and half-life ($t_{1/2}$).

ke = 0.00293(CrCl) + 0.014 = 0.00293(117 mL/min) + 0.014 = **0.357** h^{-1}

$t_{1/2}$ = 0.693/ke = 0.693/0.357 h−1 = **1.9 h**

3. Estimate volume of distribution (V).

The patient is **obese**, so the volume of distribution would be estimated using the following formula:

Vd = 0.26[IBW+ 0.4(TBW− IBW)] = 0.26[57 kg + 0.4(150 kg − 57 kg)] = **24.5 L**

4. Choose desired steady-state serum concentrations.

Intra-abdominal (Cssmax) = 5–7 µg/mL; (Cssmin) <2 µg/mL to avoid toxicity. Set **Cssmax = 6 µg/mL and Cssmin = 0.5 µg/mL.**

5. Use intermittent intravenous infusion equations to compute dose

5.A. Calculate required dosage interval (τ) using a 1-hour infusion:

τ= [(ln Cssmax − ln Cssmin) / ke] + t′

τ= [(ln 6 µg/mL − ln 0.5 µg/mL) / 0.357 h^{-1}] + 1 h = **8 h**

5.B. Calculate required dose rate or rate of infusion:

$k_0 = Css_{max}.k_e.Vd[(1 - e^{-ke.\tau}) / (1 - e^{-ke.t'})]$

k_0 = (6 mg/L · 0.357 h^{-1} · 24.5 L){[1 − $e^{-(0.357\ h-1)(8\ h)}$] / [1 − $e^{-(0.357\ h-1)(1\ h)}$]} = **165 mg**

The prescribed maintenance dose would be 165 mg every 8 hours.

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

LD = k0 / (1 − $e^{-ke.\tau}$) = 165 mg / [1 − $e^{-(0.357\ h-1)(8\ h)}$] = **175 mg**

Note: this loading dose ≈10% >or< M. Dose and **wouldn't be given to the patient.**

Example 3 JM is a 20-year-old, 76-kg (height = 5 ft 8 in) male with a gram-negative pneumonia. His current serum creatinine is 1.1 mg/dL and is stable. Compute a tobramycin dose for this patient **using extended-interval dosing.**

1. Estimate creatinine clearance.

This patient is **not obese**

IBW_{males} = 50 +2.3(Ht − 60 in) = 50 + 2.3(68 − 60) = **68 kg**;

% overweight = [100(76 kg − 68 kg)] / 68kg **=12%.** **=0.12 <1.2 IBW** so The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= [(140 − age)BW] / (72 · SCr) = [(140 − 20 y)76 kg] / (72 · 1.1 mg/dL) = **115 mL/min.**

2. Estimate elimination rate constant (ke) and half-life ($t_{1/2}$).

$ke = 0.00293(CrCl) + 0.014 = 0.00293(115\ mL/min) + 0.014 = 0.351\ h^{-1}$

$t_{1/2} = 0.693 / ke = 0.693 / 0.351\ h^{-1} = 2.0\ h$

3. Estimate volume of distribution (V).

$Vd = 0.26\ L/kg\ (76\ kg) = 19.8\ L$

4. Choose desired steady-state serum concentrations.

Gram-negative pneumonia patients treated with extended-interval aminoglycoside antibiotics require (Cssmax) = 20–30 µg/mL; & (Cssmin) <1 µg/mL to avoid toxicity.

Set Cssmax = 30 µg/mL and Cssmin = 0.1 µg/mL.

5. Use intermittent intravenous infusion equations to compute dose.

5.A. Calculate required dosage interval (τ) using a 1-hour infusion:

$\tau = [(\ln Cssmax - \ln Cssmin)/ke] + t' = [(\ln 30\ \mu g/mL - \ln 0.1\ \mu g/mL) / 0.351\ h^{-1}] + 1\ h =$

$\tau = 17.3\ h \approx 24hr$

Note: Dosage intervals for extended-interval dosing should be rounded to clinically acceptable intervals of 24 hours, 36 hours, 48 hours, 60 hours, 72 hours, and multiples of 24 hours thereafter,

5.B. Calculate required dose rate or rate of infusion:

$k_0 = Css_{max.}k_e.Vd[(1 - e^{-ke.\tau}) / (1 - e^{-ke.t'})]$

$k_0 = (30\ mg/L \cdot 0.351\ h^{-1} * 19.8\ L)\{[1 - e^{-(0.351\ h-1)(24\ h)}] / [1 - e^{-(0.351\ h-1)(1\ h)}]\} = 704\ mg$

$k_0 = \approx 700mg$

The prescribed maintenance dose would be 700 mg every 24 hours.

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

$LD = k0 / (1 - e^{-ke\tau}) = 700\ mg / [1 - e^{-(0.351\ h-1)(24\ h)}] = 700\ mg$

Note: this loading dose ≈10% >or< M. Dose and **wouldn't be given to the patient.**

2- Hull and Sarubbi Nomogram Method

-For patients who **do not have disease states** or conditions that alter volume of distribution,

- The Hull and Sarubbi aminoglycoside dosing nomogram is a **quick and efficient** way to apply pharmacokinetic dosing concepts without using complicated pharmacokinetic equations

TABLE 4-3 Aminoglycoside Dosage Chart (Adapted from Sarubbi and Hull[45])

1. Compute patient's creatinine clearance (CrCl) using Cockcroft-Gault method: CrCl = [(140 − age)BW] / (S_{Cr} × 72). Multiply by 0.85 for females. Use Salazar-Cocoran method if weight >30% above IBW.
2. Use patient's weight if within 30% of IBW, otherwise use adjusted dosing weight = IBW + [0.40(TBW − IBW)]
3. Select loading dose in mg/kg to provide peak serum concentrations in range listed below for the desired aminoglycoside antibiotic:

AMINOGLYCOSIDE	USUAL LOADING DOSES	EXPECTED PEAK SERUM CONCENTRATIONS
Tobramycin Gentamicin Netilmicin	1.5–2.0 mg/kg	4–10 µg/mL
Amikacin Kanamycin	5.0–7.5 mg/kg	15–30 µg/mL

4. Select maintenance dose (as percentage of loading dose) to continue peak serum concentrations indicated above according to desired dosage interval and the patient's creatinine clearance. To maintain usual peak/trough ratio, use dosage intervals in clear areas.

Percentage of Loading Dose Required for Dosage Interval Selected

CrCl (mL/min)	EST. HALF-LIFE (HOURS)	8 HOURS (%)	12 HOURS (%)	24 HOURS (%)
>90	2–3	90	–	–
90	3.1	84	–	–
80	3.4	80	91	–
70	3.9	76	88	–
60	4.5	71	84	–
50	5.3	65	79	–
40	6.5	57	72	92
30	8.4	48	63	86
25	9.9	43	57	81
20	11.9	37	50	75
17	13.6	33	46	70
15	15.1	31	42	67
12	17.9	27	37	61
10*	20.4	24	34	56
7*	25.9	19	28	47
5*	31.5	16	23	41
2*	46.8	11	16	30
0*	69.3	8	11	21

*Dosing for patients with CrCl ≤10 mL/min should be assisted by measuring serum concentrations.

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. Estimate creatinine clearance.

This patient is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= [(140 − age)BW] / (72 · SCr) = [(140 − 50 y)70 kg] / (72 * 3.5 mg/dL) =25 mL/min

2. Choose desired steady-state serum concentrations.

Gram-negative pneumonia patients treated with aminoglycoside antibiotics require (Cssmax) = 8–10 µg/mL.

3. Select loading dose (Table 4-3).

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

LD = 2 mg/kg(70 kg) = 140 mg

4. Determine estimated half-life, maintenance dose, and dosage interval.

From the nomogram the estimated half-life is 9.9 hours, the maintenance dose (MD) is 81% of LD [MD = 0.81(140 mg) = 113 mg], and the dosage interval is 24 hours.

3-Hartford Nomogram Method for Extended-Interval Dosing

Extended-interval dosing is now a mainstream method used to administer aminoglycoside antibiotics. Conventional dosing is still preferred for endocarditis patients because the aminoglycoside is usually used for antibiotic synergy. Extended-interval doses obtained from the literature for patients with normal renal function are 4–7 mg/kg/d for gentamicin, tobramycin, or netilmicin and 11–20 mg/kg/d for amikacin.

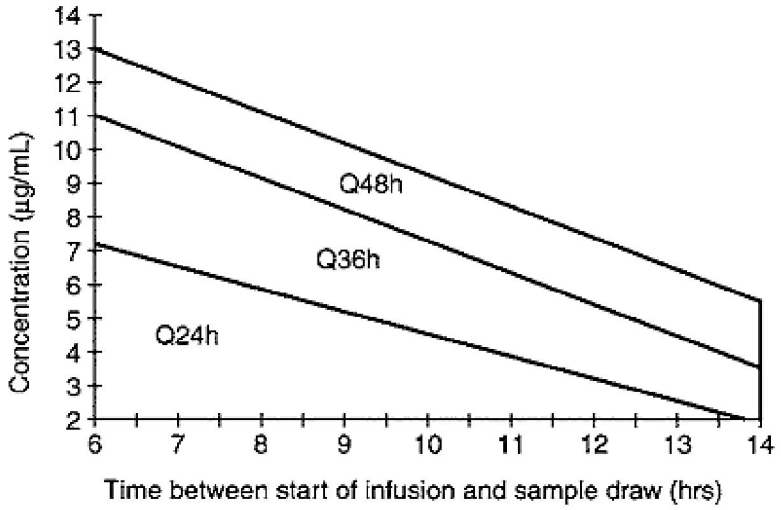
ODA nomogram for gentamicin and tobramycin at 7 mg/kg.

1. Administer 7-mg/kg gentamicin with initial dosage interval:

ESTIMATED CrCl	INITIAL DOSAGE INTERVAL
≥60 mL/min	q24 h
40–59 mL/min	q36 h
20–39 mL/min	q48 h
<20 mL/min	monitor serial concentrations and administer next dose when <1 µg/mL

2. Obtain timed serum concentration, 6–14 hours after dose (ideally first dose).
3. Alter dosage interval to that indicated by the nomogram zone (above q48 h zone, monitor serial concentrations, and administer next dose when <1 µg/mL).

TABLE 4-4 Hartford Nomogram for Extended-Interval Aminoglycosides (Adapted from Nicolau, et al[3])



Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. Compute a gentamicin dose for this patient using conventional dosing.

1. Estimate creatinine clearance.

This patient is **not obese**. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= [(140 − age)BW] / (72 · SCr) = [(140 − 50 y)70 kg] / (72 * 3.5 mg/dL) **=25 mL/min**

2. Compute initial dose and dosage interval (Table 4-4)

A dose (D) of **7 mg/kg** will provide a peak concentration >20 µg/mL.

D = 7 mg/kg(70 kg) = **490 mg**

Dosage interval would be **48 hours** using the **nomogram**.

Note: Extended-interval aminoglycoside doses should be rounded to the nearest 10–50 mg.

The prescribed maintenance dose would be 500 mg every 48 hours.

3. Select loading dose (Table 4-3).

A loading dose (LD) of 2 mg/kg will provide a peak concentration of 8–10 µg/mL.

LD = 2 mg/kg(70 kg) **= 140 mg**

3. Determine dosage interval using serum concentration monitoring. If A gentamicin serum concentration measured 13 hours after the dose equals 9 µg/mL.

Based on the nomogram, a dosage interval of **48 hours is too short** and serial concentrations should be monitored.

When the gentamicin serum concentration is <1 µg/mL, the next dose can be given.

Based on the patient's estimated elimination rate constant

ke = 0.00293(CrCl) + 0.014 = 0.00293(25 mL/min) + 0.014 = 0.087 h^{-1}

; $t_{1/2}$ =0.693/ke = 0.693 / 0.087 $^{h^{-1}}$= 8 h

Note: Some clinicians prefer to avoid the use of extended-interval dosing beyond a dosage interval of 48 hours because serum aminoglycoside concentrations can be below the MIC

Literature-Based Recommended Dosing

- **It involves the use of standard aminoglycoside doses for pediatric patients. Computation of these doses was originally based on the pharmacokinetic dosing methods.**
- **Neonates if Doses < 10 mg →rounded to the nearest tenth of a milligram.**
- **If serum creatinine values are available, estimated creatinine clearance can be computed using equations that are specific for pediatric patients**
  [age 0–1 year, CrCl(mL/min/1.73 m^2)) = (0.45 · Ht) / SCr]
  [age 1–20 years, CrCl(mL/min/1.73 m^2)) = (0.55 · Ht) / SCr]
  where Ht is in cm and SCr is in mg/dL.

Example 1 MM is a 3-day-old, 1015-g male with suspected neonatal sepsis. His serum creatinine has not been measured, but it is assumed that it is typical for his age and weight. Compute an initial gentamicin dose for this patient.

1. Compute initial dose and dosage interval.

Often, serum creatinine measurements are not available for initial dosage computation in neonates. The dosage recommendations for this population assume typical renal function, so it is important to verify that the assumption is valid.

-For this age and weight category should receive gentamicin 2.5 mg/kg every 18–24 hours.

AMINOGLYCOSIDE	ROUTE	AGE 0–4 WEEK OLD	AGE <1 WEEK OLD		AGE ≥ 1 WEEK OLD	
		WEIGHT <1200 g	WEIGHT 1200–2000 g	WEIGHT >2000 g	WEIGHT 1200–2000 g	WEIGHT >2000 g
Amikacin	IV, IM	7.5 mg/kg every 18–24 hours	7.5 mg/kg every 12 hours	7.5–10 mg/kg every 12 hours	7.5–10 mg/kg every 8 or 12 hours	10 mg/kg every 8 hours
Gentamicin or Tobramycin	IV, IM	2.5 mg/kg every 18–24 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 12 hours	2.5 mg/kg every 8 or 12 hours	2.5 mg/kg every 8 hours

Dose = 2.5 mg/kg(1.015 kg) = 2.5 mg. The prescribed dose would be 2.5 mg every 24 hours.

USE OF AMINOGLYCOSIDE SERUM CONCENTRATIONS TO ALTER DOSAGES

❶ 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: $D_{new} / C_{ss,new} = D_{old} / C_{ss,old}$ or $D_{new} = (C_{ss,new} / C_{ss,old})D_{old}$

Example ZW is a 35-year-old, 150-kg (5 ft 5 in) female with an intra-abdominal infection. Her current serum creatinine is 1.1 mg/dL and is stable. A tobramycin dose of 165 mg every 8 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 6 µg/mL and 0.5 µg/mL, respectively. After the fifth dose, steady-state peak and trough concentrations were measured and were 4 µg/mL and <0.5 µg/mL (e.g., below assay limits), respectively. Calculate a new tobramycin dose that would provide a steady-state peak of 6 µg/mL.

1. Estimate creatinine clearance.

This patient is obese

[IBWfemales (in kg) = 45 +2.3(Ht – 60) = 45 + 2.3(65 in – 60) = 57 kg].

150/57= 263% of IDW

The Salazar and Corcoran equation can beused to estimate creatinine clearance:

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - 35\ y)\{(0.287 \cdot 150\ kg) + [9.74 \cdot (1.65\ m)^2]\}}{(60 \cdot 1.1\ mg/dL)} = 117\ mL/min$$

2. Estimate elimination rate constant (ke) and half-life (t1/2).

k_e = 0.00293(CrCl) + 0.014 = 0.00293(117 mL/min) + 0.014 = 0.357 h^{-1}

$t_{1/2}$ = 0.693 / ke = 0.693 / 0.357 h^{-1} = 1.9 h

Because the patient has been receiving tobramycin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. Compute new dose to achieve desired serum concentration.

D_{new} = $(C_{ss,new} / C_{ss,old})D_{old}$ = (6 µg/mL / 4 µg/mL)* 165 mg = 247 mg, round to 250 mg

The new suggested dose would be 250 mg every 8 hours to be started at next scheduled dosing time.

4. Check steady-state trough concentration for new dosage regimen.

Css,new = (Dnew / Dold)Css,old = (250 mg / 165 mg) 0.5 µg/mL = 0.8 µg/mL

it is <1.5mg/L so it is safe

❷Pharmacokinetic Concepts Method

Example 1 JM is a 50-year-old, 70-kg (5 ft 10 in) male with gram-negative pneumonia. His current serum creatinine is 3.5 mg/dL, and it has been stable over the last 5 days since admission. A gentamicin dose of 115 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 µg/mL and <2 µg/mL, respectively. After the third dose, steady-state peak and trough concentrations were measured and were 12 µg/mL and 3.5 µg/mL, respectively. Calculate a new gentamicin dose that would provide a steady-state peak of 9 µg/mL and a trough of <2 µg/mL.

1. Estimate creatinine clearance.

This patient is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= [(140 – age)BW] / (72 · SCr) = [(140 – 50 y)70 kg] / (72 · 3.5 mg/dL)= 25 mL/min

2. Estimate elimination rate constant (k_e) and half-life ($t_{1/2}$).

The elimination rate constant versus creatinine clearance relationship is used to estimate the gentamicin elimination rate for this patient:

k_e = 0.00293(CrCl) + 0.014 = 0.00293(25 mL/min) + 0.014 = 0.087 h^{-1}

$t_{1/2}$ = 0.693 / ke = 0.693 / 0.087 h^{-1} = 8 h

Because the patient has been receiving gentamicin for more than 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. Use Pharmacokinetic Concepts method to compute a new dose.

1. Draw a rough sketch of the serum concentration/time curve by hand, keeping tract of the relative time between the serum concentrations

2. Since the patient is at steady state, the trough concentration can be extrapolated to the next trough value time

3. Draw the elimination curve between the steady-state peak concentration and the extrapolated trough concentration. Use this line to estimate half-life.

Note:

1-Determine no. of half lives:

12mg/l → 6mg/dl → 3.5mg/dl ≈ 2half lives

2- determine magnitude of half life from change plasma conc from c_{max} to C_{min}

A) Find Δ T =24hours between c_{max} to C_{min}

B) Half life will be 24hr/ 2 =12 hr the half life

3- determine new taw

A. Determine time required to decline from new c_{max} to c_{min} using founded t0.5

9mg/dl → 4.5mg/dl →2.3mg/dl →1.2mg/dl no. of half lives =3 t0.5

B . calculate new taw

3t0.5= 3*12hr= 36 hours new taw

4- determine new dose

A- Find ΔC old & ΔC new

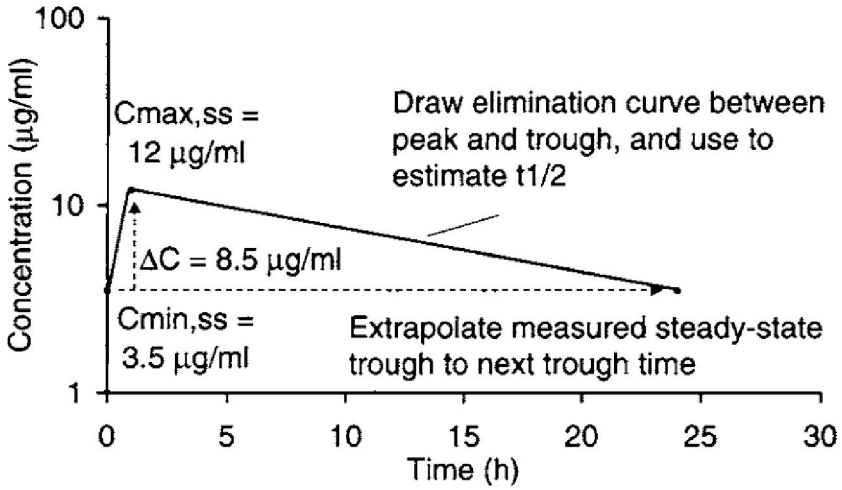
ΔC old=12 - 3.5=8.5mg/dl

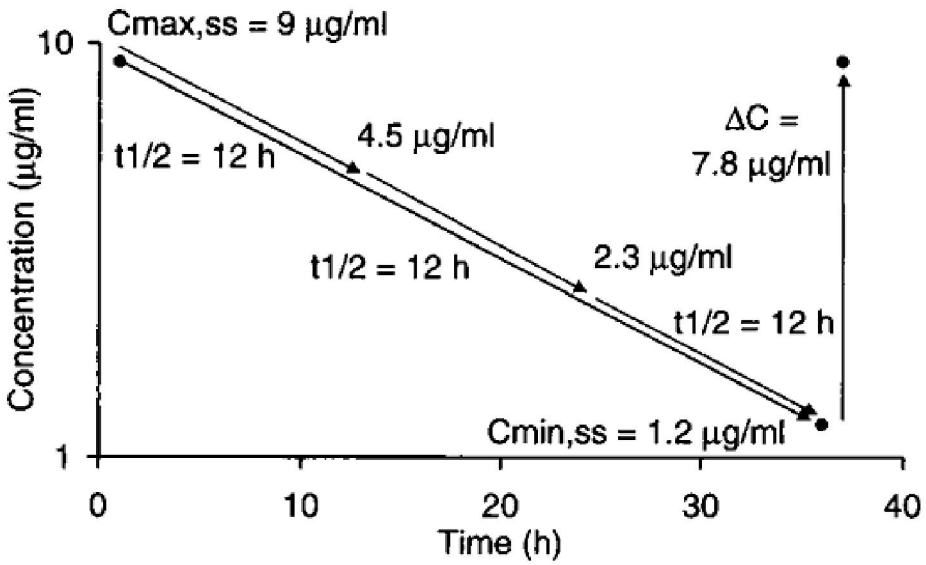
ΔC new =9-1.2 =7.8mg/dl

B- calculate new dose using $D_{new} = (\Delta C_{new} / \Delta C_{old})D_{old}$

D_{new} = (7.8 µg/mL / 8.5 µg/mL) 115 mg = 105 mg.

Gentamicin 105 mg every 36hours





❸ Sawchuk-Zaske Method

1-The Sawchuk-Zaske method was among the first techniques available to change doses using serum concentrations.

2-It allows the computation of an individual's own, unique pharmacokinetic constants and uses those to calculate a dose to achieve desired aminoglycoside concentrations.

3-The standard Sawchuk-Zaske method needs using 3–4 aminoglycoside serum concentrations obtained during a dosage interval.

4-It does not require steady-state conditions.

5- The Sawchuk-Zaske method has used to dose vancomycin and theophylline.

A- STANDARD SAWCHUK-ZASKE METHOD

Requirements

- **Cmax(immediately after a 1-hour infusion or 1/2 hour after a 1/2-hour infusion)& Cmin is obtained before next a dose,**
- **1–2 additional postdose serum aminoglycoside concentrations should be obtained at least 1 estimated half-life from each other to minimize the influence of assay error.**

The postdose serum concentrations are used to calculate the aminoglycoside elimination rate constant and half-life. $ke = 0.693/t_{1/2}$. Or by using this equation $ke = (\ln C_1 - \ln C_2) / \Delta t$ for post dose points.

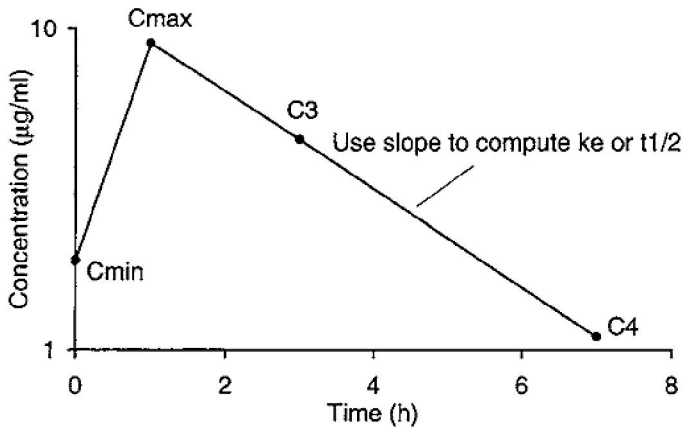


FIGURE 4-10 The Sawchuk-Zaske method for individualization of aminoglycoside doses uses a trough (C_{min}), peak (C_{max}), and 1–2 additional postdose concentrations (C_3, C_4) to compute a patient's own, unique pharmacokinetic parameters. This version of the Sawchuk-Zaske method does not require steady-state conditions. The peak and trough concentrations are used to calculate the volume of distribution, and the postdose concentrations (C_{max}, C_3, C_4) are used to compute half-life. Once volume of distribution and half-life have been measured, they can be used to compute the exact dose needed to achieve desired aminoglycoside concentrations.

VD calculation

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{min} e^{-k_e t'})]}$$

B- STEADY-STATE SAWCHUK-ZASKE METHOD: PEAK/TROUGH VERSION

If a steady-state peak and trough aminoglycoside concentration pair is available for a patient, use following equation

ke = (ln Cssmax – ln Cssmin)/τ– t'

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

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{min} e^{-k_e t'})]}$$

C- STEADY-STATE SAWCHUK-ZASKE METHOD: TWO POSTDOSE CONCENTRATIONS VERSION

Sometimes, steady-state trough concentrations will be below the assay limit or it is not possible to measure a predose concentration. Use

$ke = (\ln C1 - \ln C2)/\Delta t$, where

-C1 and C2 are the first and second steady-state postdose concentrations and

Δt is the time that expired between the two concentrations.

$Css_{max} = C1 / (e^{-ket})$, where

C1 is the first measured steady-state concentration,

ke is the elimination rate constant, and

t is the time between C1 and Css_{max};

$Css_{min} = C_2 e^{-ket}$, where

C2 is the second measured steady-state concentration,

ke is the elimination rate constant, and

t is the time between C2 and Css_{min}.

The volume of distribution (V) is calculated using the following equation:

$$V = \frac{D/t'\,(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{min} e^{-k_e t'})]}$$

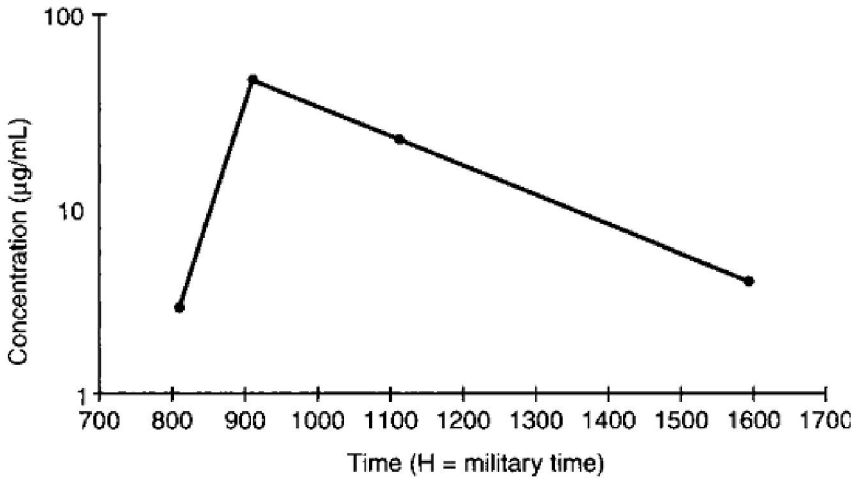
Example 1 JH is a 24-year-old, 70-kg (6 ft 0 in) male with gram-negative pneumonia. His current serum creatinine is 1.0 mg/dL, and it has been stable over the last 7 days since admission. An amikacin dose of 400 mg every 8 hours was prescribed. After the third dose, the following amikacin serum concentrations were obtained:

TIME	AMIKACIN CONCENTRATION (µg/mL)
0800 H	2.0
0800–0900 H	Amikacin 400 mg
0900 H	22.1
1100 H	11.9
1600 H	2.5

Medication administration sheets were checked, and the previous dose was given 2 hours early (2200 H the previous day). Because of this, it is known that the patient is not at steady state. Calculate a new amikacin dose that would provide a steady-state peak of 28 µg/mL and a trough between 3 µg/mL.

Use Sawchuk-Zaske method to compute a new dose.

1. Plot serum concentration/time data .



2. Because serum concentrations decrease in a straight line, use any two postdose concentrations to compute the patient's elimination rate constant and half-life.

   ke = (ln Cssmax – ln Cssmin)/τ– t'= (ln 22.1 µg/mL – ln 2.5 µg/mL) / (16 H – 09 H) = 0.311 h–1

   $t_{1/2}$ = 0.693 / ke = 0.693 / 0.311 h–1 = 2.2 h

3. Compute the patient's volume of distribution.

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(400\ mg/1h)[1 - e^{-(0.311\ h^{-1})(1\ h)}]}{0.311\ h^{-1}\{22.1\ mg/L - [2.0\ mg/L\ e^{-(0.311\ h^{-1})(1\ h)}]\}}$$

$$V = 16.7\ L$$

4. Choose new steady-state peak and trough concentrations.

Use Cmax 28 µg/mL and Cmin=3 µg/mL,

5. Determine the new dosage interval for the desired concentrations.

τ= [(ln Cssmax – ln Cssmin) / ke] + t'= [(ln 28 µg/mL – ln 3 µg/mL) / 0.311 h–1] + 1 h = 8h

6. Determine the new dose for the desired concentrations.

The dose is computed using the one-compartment model intravenous infusion equation

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

$$k_0 = (28 \text{ mg/L} \cdot 0.311 \text{ h}^{-1} \cdot 16.7 \text{ L})\{[1 - e^{-(0.311 \text{ h}^{-1})(8 \text{ h})}] / [1 - e^{-(0.311 \text{ h}^{-1})(1 \text{ h})}]\}$$

= 499 mg, rounded to 500 mg

A dose of amikacin 500 mg every 8 hours would be prescribed to begin 8 hours afterthe last dose of the previous regimen.

Example PL is a 52-year-old, 67-kg (5 ft 6 in) female with neutropenia and gram negative sepsis. Her current serum creatinine is 1.5 mg/dL, and it has been stable over the last 5 days. A gentamicin dose of 110 mg every 12 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 8–10 µg/mL and <2 µg/mL, respectively. After the third dose, steady-state concentrations were measured and were 3.8 µg/mL 1 hour after the end of a 1-hour infusion and 1.6 µg/mL 4 hours after the first concentration. Calculate a new gentamicin dose that would provide a steady-state peak of 9 µg/mL and a trough <2 µg/mL.

1. Estimate creatinine clearance.

This patient is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= {[(140 – age)BW]0.85} / (72 · SCr) = {[(140 – 52 y)67 kg]0.85} / (72 · 1.5 mg/dL)

CrCl=46 mL/min

2. Estimate elimination rate constant (ke) and half-life (t1/2).

ke = 0.00293(CrCl) + 0.014 = 0.00293(46 mL/min) + 0.014 = 0.149 h^{-1}

$t_{1/2}$ = 0.693 / ke = 0.693 / 0.149 $^{h-1}$= 4.7 h

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. Use Steady-state Sawchuk-Zaske method to compute a new dose.

1. Compute the patient's actual 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 C1 – ln C2) / Δt = (ln 3.8 µg/mL – ln 1.6 µg/mL) / (4 h) = 0.216 h^{-1}

$t_{1/2}$ = 0.693 / ke = 0.693 / 0.216 h^{-1} = 3.2 h

2. Extrapolate measured concentrations to steady-state peak and trough values.

Css_{max} = C1 / (e^{-ket}) = (3.8 µg/mL) / [$e^{-(0.216\ h-1)(1\ h)}$] = 4.7 µg/mL

Css_{min} = C_2e^{-ket}= (1.6 µg/mL)[e−(0.216 h−1)(6 h)] = 0.4 µg/mL

3. Compute the patient's volume of distribution.

$$V = \frac{D/t'(1 - e^{-k_e t'})}{k_e[Css_{max} - (Css_{min} e^{-k_e t'})]} = \frac{(110\ mg/1\ h)[1 - e^{-(0.216\ h^{-1})(1\ h)}]}{0.216\ h^{-1}\{4.7\ mg/L - [0.4\ mg/L\ e^{-(0.216\ h^{-1})(1\ h)}]\}}$$

Vd=22.6 L

4. Choose new steady-state peak and trough concentrations.

Css_{max} =9 µg/mL Css_{min} =and 1.5 µg/mL,

5. Determine the new dosage interval for the desired concentrations.

τ= [(ln Cssmax − ln Cssmin) / ke] + t'= [(ln 9 µg/mL − ln 1.5 µg/mL) / 0.216 h^{-1}] + 1 h

= 9.3 h, rounded to 8 h

6. Determine the new dose for the desired concentrations.

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

$$k_0 = (9\ mg/L \cdot 0.216\ h^{-1} \cdot 22.6\ L)\{[1 - e^{-(0.216\ h^{-1})(8\ h)}] / [1 - e^{-(0.216\ h^{-1})(1\ h)}]\}$$

k0 = 186 mg, rounded to 185 mg

A dose of gentamicin 185 mg every 8 hours would be prescribed to begin approximately 8 hours after the last dose of the current regimen.

❹Area Under the Curve (AUC) Method

- **(AUC) is the best measurement of total exposure to a drug, and some clinicians recommend adjustment of aminoglycoside doses so that target steady-state AUC values are achieved instead of altering doses to attain target steady state peak and trough concentrations.**
- **Most often, the AUC method is used with extended-interval aminoglycoside dosing.**
- **The steady-state area under the concentration-time curve during the dosage interval (AUCss) is computed using the following equation:**

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{C_{max,ss} - C_{min,ss}}{k_e}\right)$$

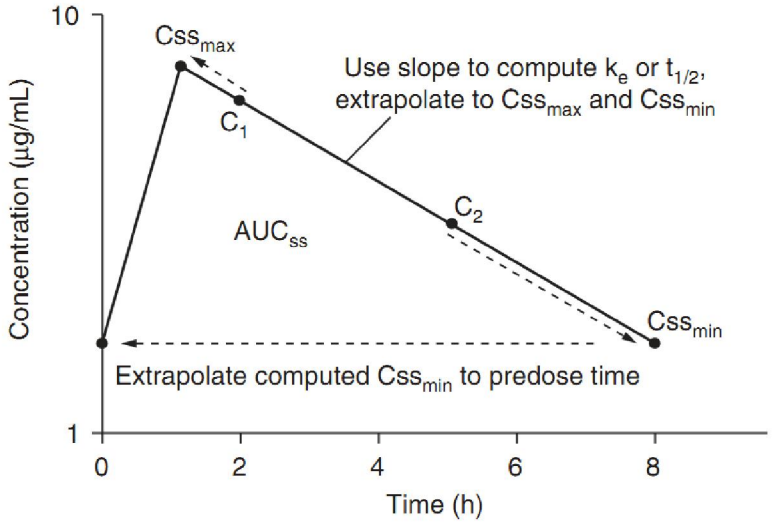


FIGURE 4-14 The Area Under the Curve (AUC) method uses two postdose concentrations (C_1 and C_2) to individualize aminoglycoside therapy. Once the concentrations are obtained, they are extrapolated either mathematically or graphically to determine steady-state peak and trough values. The elimination rate constant is calculated using the measured concentrations: $k_e = (\ln C_1 - \ln C_2) / \Delta t$, where C_1 and C_2 are the first and second steady-state postdose concentrations and Δt is the time that expired between the two concentrations. Steady-state peak and trough concentrations are calculated using the following equations: $Css_{max} = C_1 / (e^{-k_e t})$, where C_1 is the first measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_1 and Css_{max}; $Css_{min} = C_2 e^{-k_e t}$, where C_2 is the second measured steady-state concentration, k_e is the elimination rate constant, and t is the time between C_2 and Css_{min}. The steady-state area under the concentration-time curve during the dosage interval (AUC_{ss}) is computed using the following equation:

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{Css_{max} - Css_{min}}{k_e} \right)$$

Example 1 **KE is a 23-year-old, 59-kg (5 ft 4 in) female with salpingitis. Her current serum creatinine is 0.6 mg/dL, and it has been stable over the last 3 days. A gentamicin dose of 250 mg every 24 hours was prescribed and expected to achieve steady-state peak and trough concentrations equal to 25 µg/mL and <1 µg/mL, respectively. After the third dose, steady-state concentrations were measured and equaled 9.6 µg/mL 2 hours after the end of a 1-hour infusion and 2.6 µg/mL 6 hours after the end of infusion. Calculate a new gentamicin dose that would provide a steady-state AUC of 81 (mg · h)/L.**

1. Estimate creatinine clearance.

This patient is not obese. The Cockcroft-Gault equation can be used to estimate creatinine clearance:

CrCl= {[(140 – age)BW]0.85} / (72 · SCr) = {[(140 – 23 y)59 kg]0.85} / (72 · 0.6 mg/dL)

CrCl= 136 mL/min

2. Estimate elimination rate constant (ke) and half-life (t1/2).

ke = 0.00293(CrCl) + 0.014 = 0.00293(136 mL/min) + 0.014 = 0.413 h^{-1}

$t_{1/2}$ = 0.693/ke = 0.693/0.413 h^{-1}= 1.7 h

Because the patient has been receiving gentamicin for more that 3–5 estimated half-lives, it is likely that the measured serum concentrations are steady-state values.

3. Use Steady-state AUC method to compute a new dose.

A. Compute the patient's actual 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 C1 – ln C2) / Δt = (ln 9.6 µg/mL – ln 2.6 µg/mL) / (4 h) = 0.327 h–1

$t_{1/2}$ = 0.693 / ke = 0.693 / 0.327 h–1= 2.1 h

B. Extrapolate measured concentrations to steady-state peak and trough values.

Css_{max} = C_1 / (e^{-ket}) = (9.6 µg/mL) / [$e^{-(0.327\ h-1)(2\ h)}$] = 18.5 µg/mL

Css_{min} = C_2e^{-ket} = (2.6 µg/mL)[e–(0.327 h–1)(17 h)] = 0.01 µg/mL

3. Compute the patient's AUCss

$$AUC_{ss} = \frac{Css_{max} - Css_{min}}{k_e} + \left(0.065 \cdot \frac{Css_{max} - Css_{min}}{k_e}\right)$$

$$AUC_{ss} = \frac{18.5\ mg/L - 0.01\ mg/L}{0.327\ h^{-1}} + \left(0.065 \cdot \frac{18.5\ mg/L - 0.01\ mg/L}{0.327\ h^{-1}}\right)$$

AUCss = 60.2 (mg · h)/L

4. Choose new target AUCss. (use AUC of 81 (mg · h)/L).

5. Determine the new dose for the desired AUCss.

Dnew = (AUCss,new/AUCss,old)Dold = {[81 (mg · h)/L] / [60.2 (mg · h)/L]}250 mg

Dnew = 336 mg, rounded to 350 mg

6. Determine the new steady-state peak and trough concentrations.

Css,new = (Dnew / Dold)Css,old = (350 mg / 250 mg) 18.5 µg/mL = 25.9 µg/mL for the peak

Css,new = (Dnew / Dold)Css,old = (350 mg / 250 mg) 0.01 µg/mL = 0.01 µg/mL for the trough

These steady-state peak and trough concentrations are acceptable for the infection being treated and the new prescribed dose would be 350 mg every 24 hours.

❺BAYESIAN PHARMACOKINETIC COMPUTER PROGRAMS

SPECIAL DOSING CONSIDERATIONS

Hemodialysis Dosing

Aminoglycoside antibiotics are eliminated by dialysis, so renal failure patients receiving hemodialysis must have aminoglycoside dosage regimens that take dialysis clearance into account.

Example 1 A 62-year-old, 65-kg (5 ft 8 in) male who has chronic renal failure (CRF), and receives hemodialysis three times weekly with a low-flux dialysis filter. An initial dosage regimen for tobramycin needs to be computed for a patient to achieve peak concentrations of 6–7 mg/L and postdialysis concentrations 1–2 mg/L.

Initial Dosage Determination

1. Assess Patient hydration status due to poor fluid balance during C.R.F

[IBWmale = 50 kg + 2.3(Ht − 60 in) = 50 kg + 2.3(68 − 60) = 68 kg].

Patient's real weight< IBW so it is underhydrated so use the average volume of distribution for aminoglycoside antibiotics equal to 0.26 L/kg

2. Calculate A loading dose of tobramycin would be appropriate for this patient because the expected half-life is long (~50 h)

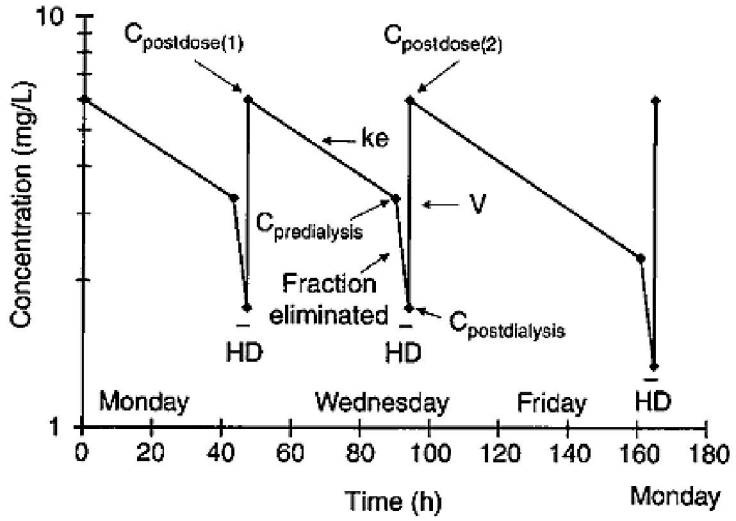


FIGURE 4-15 Concentration/time graph for tobramycin in a hemodialysis patient using estimated, population pharmacokinetic parameters. The initial dose was given postdialysis at 1400H on Monday (time = 0 h). Hemodialysis periods are shown by small horizontal bars labeled with HD, and days are indicated on the time line. In order to compute patient-specific pharmacokinetic parameters, four serum concentrations are measured. The elimination rate constant (k_e) is computed using two concentrations after dosage administration ($C_{postdose(1)}$ and $C_{predialysis}$), the fraction eliminated by dialysis by two concentrations ($C_{predialysis}$ and $C_{postdialysis}$) before and after dialysis, and the volume of distribution using two concentrations ($C_{postdialysis}$ and $C_{postdose(2)}$) after another dosage administration.

V = 0.26 L/kg · 65 kg = 16.9 L; LD = Cmax · V = 6 mg/L · 16.9 L = 101 mg, rounded to 100 mg The loading dose is to be given after hemodialysis ends at 1300 H on Monday (hemodialysis conducted on Monday, Wednesday, and Friday from 0900 – 1300 H).

3. Calculate Ke of the patient before dialysis

ke (in h^{-1}) = 0.00293 · CrCl + 0.014 = 0.00293 (0 mL/min) + 0.014 = 0.014 h^{-1}

creatinine clearance of approximately zero due to CRF

4. Calculate The expected concentration at 0900 H on Wednesday

$C = C_0e^{-ket}$, where C is the concentration at t hours after the initial concentration

C = (6 mg/L)e−(0.014 h−1)(43 h)=3.3 mg/L.

5. patient Data when is receiving hemodialysis,

During hemodialysis with a low-fluxer, the average half-life for aminoglycosides is 4 hours.

ke = 0.693/($t_{1/2}$) = 0.693/4 h = 0.173 h^{-1}

; C = C_0e^{-ket}=3 mg/L)$e^{-(0.173\ h-1)(4\ h)}$ = 1.7 mg/L. post dialysis

5. Calculate postdialysis replacement dose

This dose is given to increase the maximum concentration to its original value of 6 mg/L:

Replacement dose = (C_{max} −$C_{baseline}$)V = (6 mg/L − 1.7 mg/L)16.9 L = 73 mg, round to 75 mg (where Cmax is the maximum postdose concentration and Cbaseline is the predose concentration).

Use of Aminoglycoside Serum Concentrations to Alter Dosages

It need knowledge of individualized pharmacokinetic data of patient

A. Calculate Ke using slope of Conc time curve

ke = ($C_{postdose(1)}$− $C_{predialysis}$) /Δt, where Δt is the time between the two concentrations,

B. Calculate fraction eleiminated

fraction eliminated = [($C_{predialysis}$ − $C_{postdialysis}$) / $C_{predialysis}$]

C. Calculate Volume of distribution

[V = D / ($C_{postdose(2)}$− $C_{predialysis}$)].