Therapeutic Drug Monitoring(TDM)

The aminoglycoside antibiotics

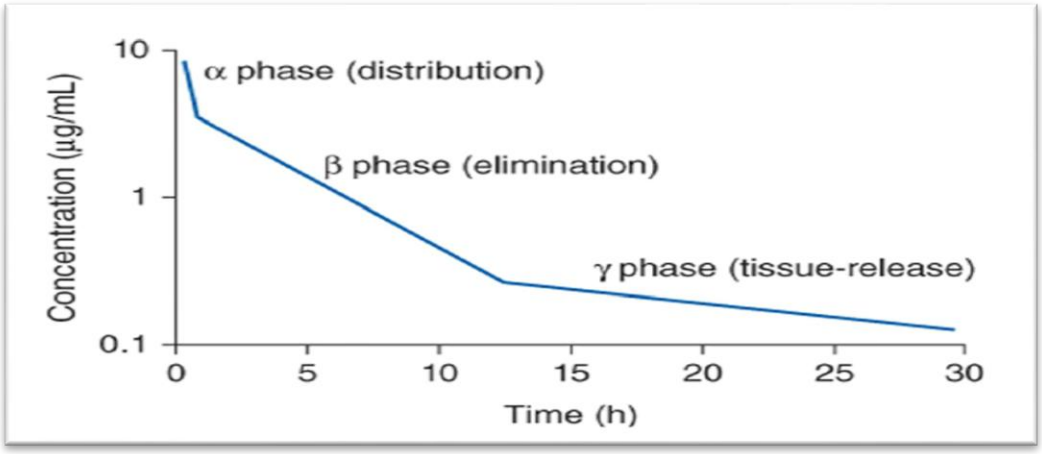
- Aminoglycoside antibiotics are bactericidal, and the drugs exhibit concentration dependent bacterial killing.
- The aminoglycosides are eliminated almost completely (≥ 90%) unchanged in the urine primarily by glomerular filtration

Concentration-efficacy relationships :

- The pharmacodynamic properties of aminoglycosides are: Concentration-dependent killing & Significant post-antibiotic effect
- Antibiotics with concentration-dependent killing characteristically kill bacteria at a faster rate when drug concentrations are higher.
- Also, aminoglycosides have a concentration-dependent post antibiotic effect. The post antibiotic effect is the phenomenon of continued bacterial killing even though serum concentrations have fallen below the minimum inhibitory concentration (MIC).
- Because the post antibiotic effect is concentration-dependent for the aminoglycosides، higher drug concentrations lead to a longer post antibiotic effect.

***Administration:**

o When given by IV infusion over 30 minutes, aminoglycosides follow a 3-compartment pharmacokinetic model; alpha (distribution), B (elimination), and gamma (tissue release) .



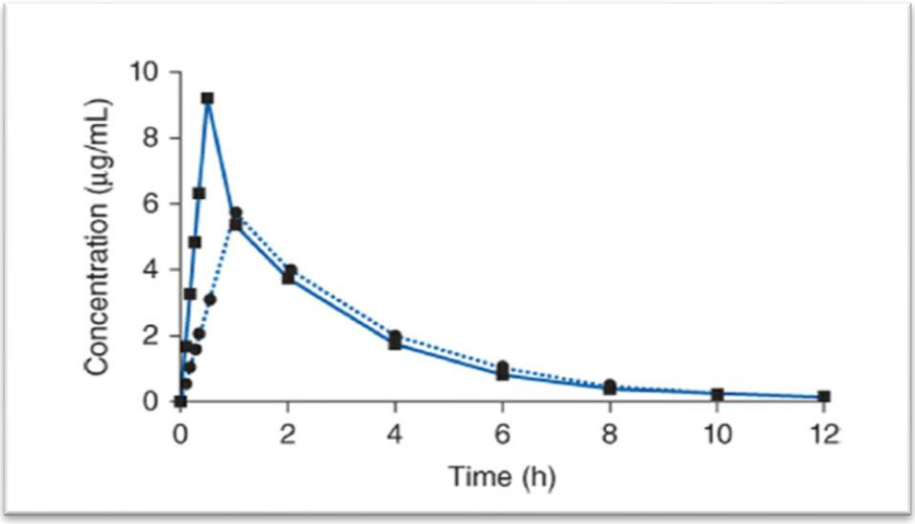
o When infused over one hour, the distribution phase is usually not observed. The gamma phase begins approximately sixteen hours post infusion**.**

o Aminoglycoside antibiotics are given as short-term (1/2-1 hour) infusions.

o Ifa l-hour infusion is used, maximum end of infusion peak" concentrations are measured when the infusion is completed ..

o Ifa 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 if a 1/2- hour infusion is used before peak concentrations are measured.

o That mean the peak always measured after 1 hr.



THERAPEUTIC AND TOXIC CONCENTRATIONS

The MIC for susceptible bacteria is higher for amikacin than it is for the other aminoglycosides. Because the pharmacokinetics is similar for all these drugs، higher doses of amikacin are needed to treat infections.

Aminoglycoside antibiotics are given by two methods:

1- **The conventional method of dosing** is to administer multiple daily

doses (usually every 8 hours) Stead-state when using conventional dosing:

A-peak concentration selection

5-10 ug/mL for gentamicin, tobramycin, or netilmicin.

15- 30 ug/mL for amikacin.

B-Steady-state trough concentration selection

< 2 ug/mL for gentamicin, tobramycin or netilmicin.

< 5 ug/mL for amikacin.

o Exceeding peak steady-state concentrations of 12-14 ug/mL for gentamicin، tobramycin, or netilmicin or 35-40 ug/mL for amikacin when using conventional dosing leads to an increased risk of ototoxicity.

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

2-**Extended-interval method** (usually the total daily dose given once per day) take advantage of concentration-dependent bacterial killing and the post antibiotic effect.

Steady-state when using extended interval dosing:

A-peak concentration selection

20-30 ug/mL for gentamicin, tobramycin, or netilmicin

B-Steady-state trough concentration selection

< 1 ug/mL

Question/ why increased toxicity is not seen in patients with extremely high peak

concentrations obtained during extended-interval dosing of aminoglycosides؟

Answer/

The hypothesized reason is that

1- both nephrotoxicity and ototoxicity are due to accumulation of aminoglycoside in the relevant tissue. 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.

2- Also, some of the uptake mechanisms into the ear and kidney may be saturable, so that high peak serum concentrations of aminoglycosides may not result in high renal or ear tissue concentrations،

Methods to initiate aminoglycoside therapy

1-The pharmacokinetic dosing method

2 -The Hull and Sarubbi nomogram

3-The Hartford nomogram

4 -Literature-based recommended dosing

1-The pharmacokinetic dosing method

-Most flexible It allows for individualized target serum concentrations to be chosen for a patient, so It can be used for both conventional and extended-interval dosing.

To calculate intial dose by pharmacokinetic dosing method

I- calculating the estimated pharmacokinetic parameter

A- Elimination rate constant estimate

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

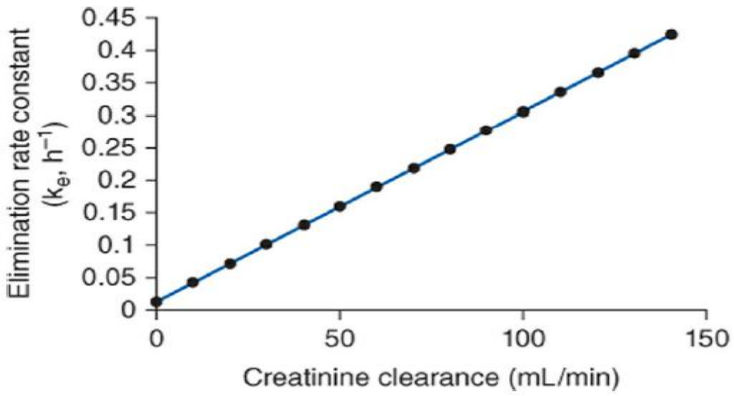


FIGURE :- Relationship between renal and aminoglycosicde climination. The elimination rate constant (k) for aminoglycoside antibiotics increases in proportion with creatinine clearance (CrCI)

B-Volume of distribution estimate

- The av. volume of distribution for patients without disease states and conditions that change this parameter is:

Vd= 0.26 L/kg.

- For cystic fibrosis patient Vd= 0.35 L/ kg
- V Ifa patient weighs less than their ideal body weight, actual body weight is used to estimate volume of distribution.
- For patients whose weight is between their ideal body weight and 30% over ideal weight, actual body weight can be used to compute estimated volume of distribution،
- In patients who are more than 30% above their IBW, (Vd) estimates should include both ideal and actual total body weighs using the following equation:

V= 0.26[IBW + 0.4(TBW – IBW)]

In patients who are overhydrated or have ascites, their dry body weight can be used to provide an improved volume of distribution estimate (V in L) using the following formula:

$$V = (0.26 \cdot DBW) + (TBW - DBW($$

II- Selection of pharmacokinetic model and equations:

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

Note:

- ❖ Loading doses should be considered for patients with creatinine clearance values below 60 mL/min.
- ❖ One approach is to use different equations depending upon the renal function of the patient so use (Intermittent intravenous infusion for creatinine clearances >30 mL/min، while Intravenous bolus for creatinine clearances <30 mL/min).
- ❖ Alternatively, intermittent intravenous infusion equations can be used for all patients regardless of renal function.

III-Steady-state concentration selection

o Severe infections, such as gram-negative pneumonia or septicemia, or infections with organisms that have a high minimum inhibitory concentration (MIC) such as Pseudomonas aeruginosa generally require peak steady-state serum concentrations of:

8-10 ug/mL for gentamicin, tobramycin, or netilmicin

25-30 ug/mL for amikacin

When using conventional dosing.

o Moderate infections at sites that are easier to penetrate or with organisms that display lower MIC values, such as intra-abdominal infections are usually treated with

5-7 ug/mL (gentamicin, tobramycin, or netilmicin)

15-25 ug/mL. (Amikacin)

o Aminoglycosides in combination with penicillin or other antibiotics for the treatment of gram positive infections such as infective endocarditis, steady-state peak concentrations of 3-5 ug/mlL for gentamicin, tobramycin, or netilmicin

12-15 ug/mL for amikacin.

o For conventional dosing, steady-state trough concentrations should be maintained

<2 ug/mL for tobramycin, gentamicin, and netilmnicin or

<5-7ug/mL for amikacin.

o For extended-interval dosing, steady-state trough concentrations should be < 1ug/mL for gentamicin, tobramycin, and netilmicin.

2- The Hull and Sarubbi nomogram

Assumptions

o target concentration ranges consistent with conventional dosing only،

o fixed volume of distribution parameter in the normal range،

o Limited dosage interval selection (no longer than 24 hours).

o Thus, it should be used only in patients who only have renal dysfunction and/or

obesity only when conventional dosing is to be used.

o Not used for extended interval dosing

o For patients who do not have disease states or conditions that alter volume of distribution, the only two patient-specific factors that change when using the pharmacokinetic dosing method is patient weight and creatinine clearance.

Because of this, it is possible to make a simple nomogram to handle uncomplicated patients with a standard volume of distribution

- **Calculation method:**

1- Compute patient's creatinine clearance (CrCI) using Cockcroft-Gault method:

CrCl= ((140 – age) BW] /(SCr x 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 (mg/kg)	Expected Peak Serum Concentrations (μg/mL)
Tobramycin Gentamicin Netilmicin	1.5-2.0	4-10
Amikacin Kanamycin	5.0-7.5	15-30

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.

CrCl (mL/min)	Est. Half-Life (h)	8 h	12 h	24 h
>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 CrCI ≤10 ml/min should be assisted by measuring serum concentrations.

3- Hartford Nomogram Method (for Extended-Interval Dosing)

o It's is designed for use when extended interval dosing is desired.

o This nomogram also incorporates a method to adjust aminoglycoside doses based on serum concentration feedback

o The most widely used extended-interval for patients with renal dysfunction which uses a

o 7-mg kg dosefor gentamicin, tobramycin, or netilmicin

o l1-20 mg/kg/d for amikacin

o Because the cystic fibrosis example requires a different volume of distribution (0.35 Lkg) and extended-interval dosing has not been adequately tested in patients with endocarditis, the Hartford nomogram should not be used in these situations

*In obese patients, adjusted body weight (ABW) should be used to compute the dose:

$$ABW = IBW + 0.4(TBW - IBW)$$

* The dosage interval is set according to the patient's creatinine clearance

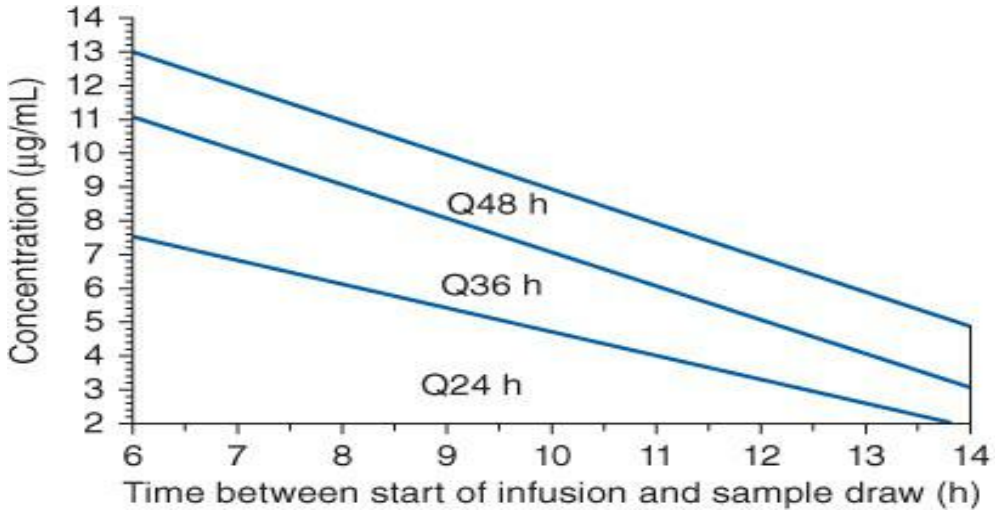
o Calculations:

1 - Administer 7-mg/kg gentamicin or 15 mg/kg for amikacin with initial dosage interval:

Estimated CrCl (mL/min)	Initial Dosage Interval
≥60	q24h
40–59	q36h
20–39	q48h
<20	Monitor serial concentrations & 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 <l ug/mL).



Hartford Nomogram

3-Literature-based recommended dosing

- Conventional dosing

3-5 mg/ kg /day for gentamycin،

15mg/ kg /day for amikicin

- Extended interval dosing

4-7 mg/kg/day for gentamycin

11-20 mg/kg/ day for amikacin

USE OF AMINOGLYCOSIDE SERUM COONCENTRATIONS TO ALTER DOSAGES

o Mean we use actual pharmacokinetics parameters to calculate the most appropriate dose for the patients using his own actual pharmacokinetics parameters

Method

1-linear pharmacokinetics

$$D_{new} / Css_{new} = D_{old} / Css_{old}$$

$$D_{new} = (Css_{new} / Css_{old}) * D_{old}$$

D is the dose, Css is the steady –state peak or trough conc.