

Aminoglycosides

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Gentamicin

Tobramycin

Amikacin
Netilmicin
Streptomycin
Kanamycin
Neomycin

...

...

.....

Excellent activity against many Gram negatives

- Causes renal and aural side effects
- Under-dosing → therapeutic failure
- PK-controlled dosing
- $CL \text{ (via GF)} = CL_{cr}$

Lower doses will help with toxicity? No! Must achieve high conc. to treat and avoid resistance

May avoid toxicity by playing around with PK of the drug ---

CL of aminoglycosides is via glomerular filtration and mirrors the clearance of creatinine

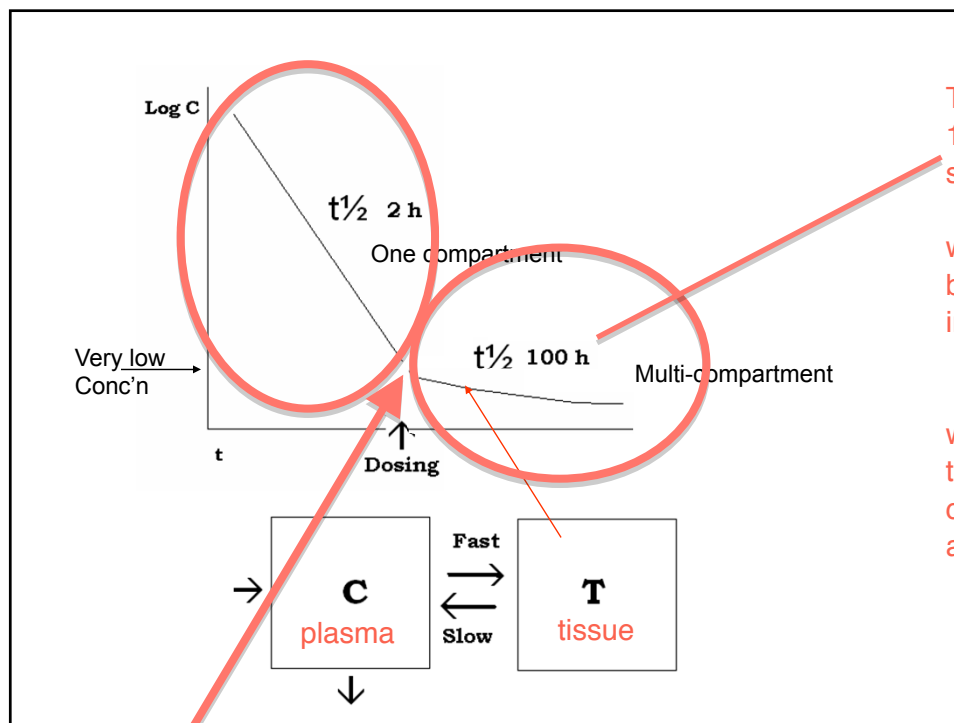
Pathophysiological Factors

- Fever: \uparrow CL
 - (\uparrow HR : \uparrow Cardiac Output)
- Sex: CL, M>F
- Burn Patients
 - \uparrow Vd (\uparrow Extravascular fluid)
 - \downarrow t $\frac{1}{2}$ (fever or Vd??)
- Cystic Fibrosis: \uparrow CL??
- Bleeding

Fever inc. clearance of AGs
inc HR and CO thus inc CL

Burn patients b/c of dehydration and later on (edema), it may affect the PK of aminoglycosides

AGs demonstrates multicompartment perfectly



Terminal half life is around 100 hours because the small dose is lingering

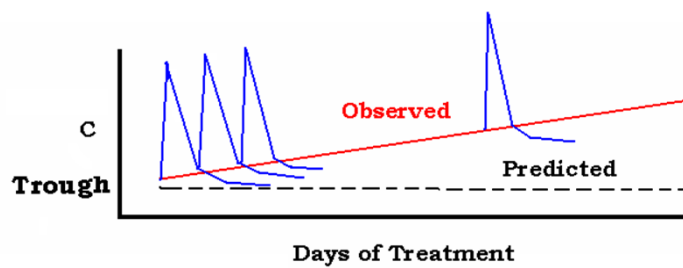
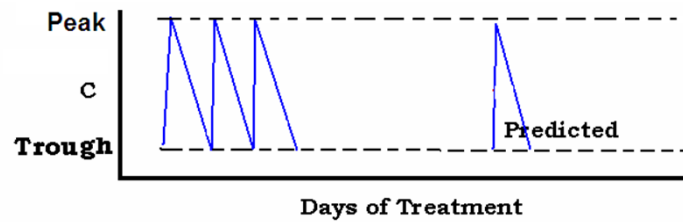
when conc. very high in blood, the drug is pushed into tissue

when the conc is lower than in tissue, the drug is coming back to the blood and creates an equilibrium

Knowing this conc (trough levels) will tell me how much drug is left in the kidneys and thus whether or not I will need to be careful

Assuming one compartment model:

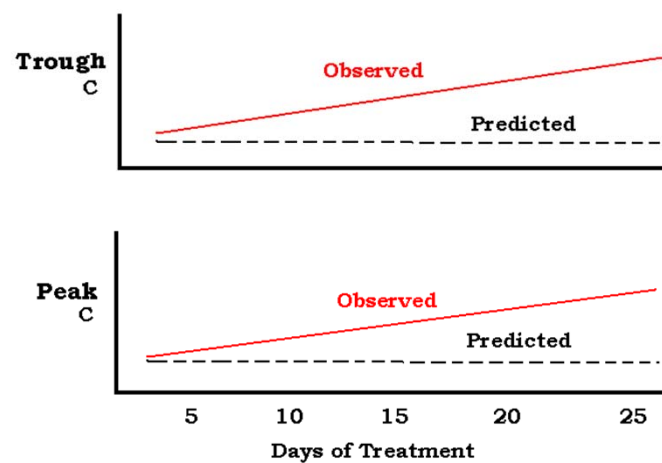
$t_{1/2}$ 2 h; τ , 8 h



Over the time of therapy
the trough conc is going
higher and higher
---> toxicity happening

Same effect is seen with
the peak conc.

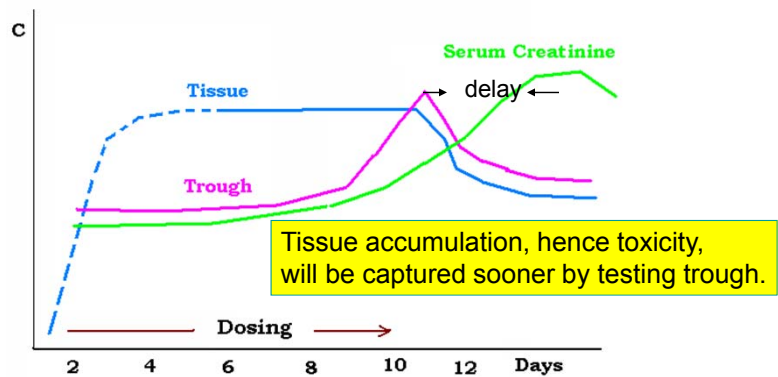
Assuming one compartment model:

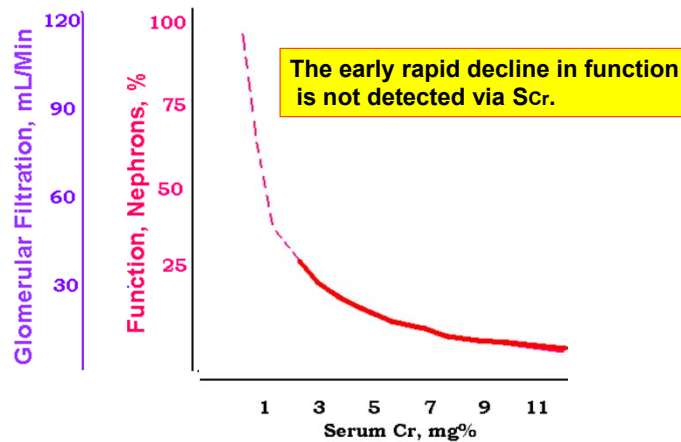


With these
drugs

Monitor:

- Peak concentration for efficacy
- Trough concentration for toxicity
- Why not creatinine for toxicity?





Risk Factors:

High tissue accumulation

Keep trough concentration below 2 mg/L

Dose

Duration of therapy

(<10 days)

Dehydration

Diuretics

Age

Other nephrotoxins

Desired Peak Serum Concentrations for Gentamicin and Tobramycin

<u>Infection</u>	<u>Desired Peak (mg/L)</u>
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You can go as high as 14 mg/L

Pneumonia, biliary tract infection, extraabdominal abscess, peritonitis, endocarditis	7-8
Wound infections, sepsis, diverticulitis	6-7
Cellulitis, pyelonephritis	5-6
Cystitis	4-5

Trough <2 mg/L

For treating pneumonia with gentamicin,

- A) keep concentration between 8 and 2 during the dosing regimen.
- B) a peak concentration of 8 followed by a decline of concentration to below 2 is desired.
- C) make sure that the trough concentration is kept at 2.

Dosing

GR Matzke ; WS Burkle; RL Lucarotti, (1983) Drug Intell. Clin. Pharm. 17:425-432.

Initial (loading dose)

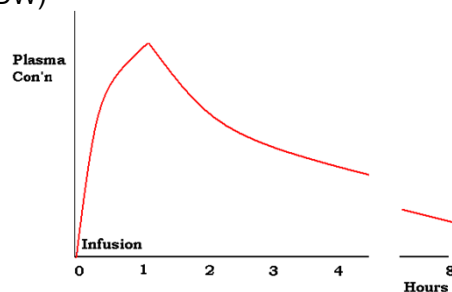
No adjustment for renal dysfunction needed.

Use dosing weight (DW):

- $DW = IBW + [(TBW - IBW) \times 0.4]$

$IBW \text{ (male)} = 0.9 \text{ H (cm)} - 88$ $IBW \text{ (female)} = 0.9 \text{ H (cm)} - 92$

- Loading Dose: 1.5-2.0 mg/kg (DW)
- Inject over 0.5 to 1 h



Maintenance dose

- Note that female Cl_{cr} amount to 85% of that of male.
- For grossly overweight patients (TBW 30% over IBW) use DW.

Maintenance dose

Based on creatinine clearance (CrCL):

Cockcroft & Gault Eq:

$$\text{CrCL (mL/min)} = \frac{140 - \text{age (yr)} \times \text{LBW (kg)}}{\text{SCr (umol/L)} \times 0.81}$$

X 0.85 for women

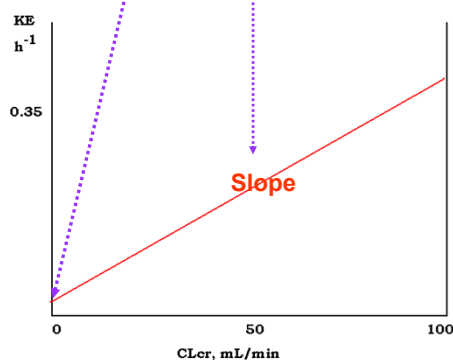
$$\text{CrCL (male)} = \frac{(140 - \text{age}) \text{ LBW}}{72 C_{cr}}$$

$$\text{CrCL (female)} = \frac{(140 - \text{age}) \text{ LBW}}{85 C_{cr}}$$

- For grossly overweight patients (TBW 30% over IBW) use DW.
- SI unit conversion factor for conc'n., 88.4 (μmol/L); for CrCL, 0.0167 (mL/s)

Estimate Drug t_{1/2}:

- Gentamicin: $\text{KE} = 0.015 + [0.00285 \times \text{Clcr (mL/min)}]$
- Tobramycin: $\text{KE} = 0.010 + [0.0031 \times \text{Clcr (mL/min)}]$



- **Estimate Drug $t_{1/2}$:**
- Gentamicin: $KE = 0.015 + (0.00285 \times Cl_{cr})$
- Tobramycin: $KE = 0.010 + (0.0031 \times Cl_{cr})$
- **Dosing time interval (τ):**
- $\tau = [-1/KE \times \ln(C_{min}/C_{max})] + t$
 - (t = time of infusion)
- **Vd:**
 - Normal; 0.2 L/kg
 - Dehydrated 0.15 L/kg
 - Overhydrated, 0.3 L/kg

Dm:

$$DM = t \left[C_{\max} V_d K_E \frac{(1 - e^{-K_E \tau})}{(1 - e^{-K_E t})} \right]$$

- Take blood samples 0-15 min post infusion (peak) and just before the next dose (trough).

Ideal body weight is much smaller than TBW so dose based on IBW

A case:

Patient: Female, 25-y-old, 172 cm (=5' 8.8"), 180 kg
Scr, 186 $\mu\text{mol/L}$ (2.1 mg%)

Infection: Gentamicin susceptible cystitis,

- $DL = 1.5 \text{ mg/kg (DW)}$
- $DW = IBW + [(TBW - IBW) \times 0.4]$ Dosing weight is IBW + 40% of TBW-IBW
- $IBW = 45.5 \text{ kg} + (2.3 \text{ kg} \times 8.8) = 65.7 \text{ kg}$
- $DW = 65.7 + (180 - 65.7) \times 0.4 = 111 \text{ kg}$
- $DL = 1.5 \times 111 = 166 \text{ mg}$

166 vs 160 mg

Infuse 160 mg over 30 min

Round to 160mg

DM:

$$\text{Clcr}_{\text{female}} = \frac{(140 - \text{AGE}) \times \text{DW (kg)} \times 0.85}{\text{Scr } (\mu\text{mol/L}) \times 0.81}$$

$$\text{Clcr} = \frac{(140 - 25) \times 111 \times 0.85}{186 \times 0.81} = 71.8 \text{ mL/min}$$

$$\text{KE} = 0.015 + (0.00285 \times \text{Clcr}) \quad \text{Rate constant for elimination}$$
$$= 0.015 + (0.00285 \times 71.8) = 0.22 \text{ h}^{-1}$$

$$\tau = [-1/\text{KE} \times \ln (\text{Cmin}/\text{Cmax})] + t$$

$$\tau = [-1/0.22 \times \ln 1/5] + 0.5 = 7.81 \text{ h}$$

From KE, calculate dosing interval

5 is the Cmax and 1 is Cmin

Choose 8 h.

Again round to 8h

$$V_d = wt \times 0.2$$

Maintenance Dose

$$DM = t \left[C_{\max} V_d K_E \frac{(1 - e^{-K_E \tau})}{(1 - e^{-K_E t})} \right]$$

- $DM = 0.5 [5(111 \times 0.2) 0.22 \times (1 - e^{-0.22 \times 8}) / (1 - e^{-0.22 \times 0.5})]$
 $= 96.6 \text{ mg}$
- Infuse 100 mg over 30 min every 8 h

Peak and trough with the rounded values: To check Cmin and Cmax with the rounded values

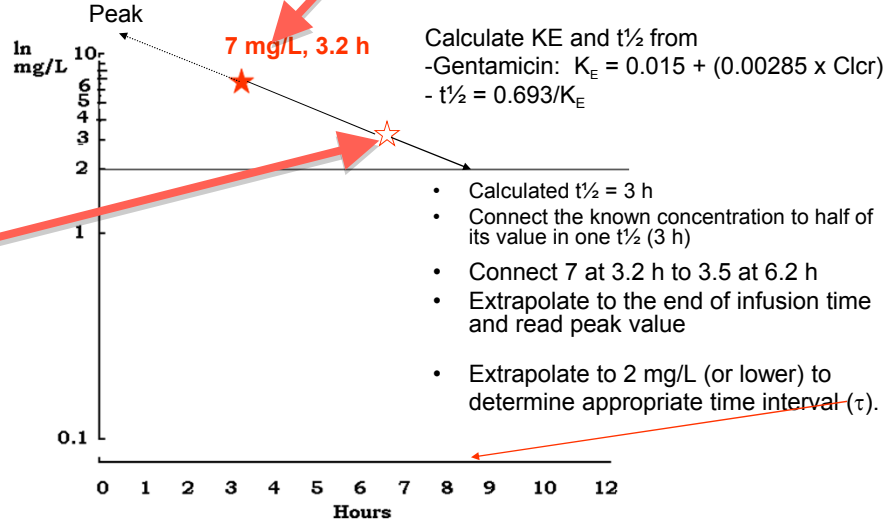
$$C_{\min} = C_{\max} \left[e^{-K_E (\tau - t)} \right] = 0.95$$

$$C_{\max} = \frac{DM}{t V_d} \frac{1 - e^{-K_E t}}{K_E (1 - e^{-K_E \tau})} = 5.12$$

This number is valuable because it is the ACTUAL blood level from the patient without making any assumptions

Dosage adjustment based on one known concentrations

(Assume 100 mg dose over 30 min)



This point here is derived from the $t_{1/2}$... it will be 3.5 after one half life (3hrs)

"Carpenter's logic"

Then extrapolate line up (to get peak) and down to see elimination

Looks like C_{min} (after 8 hours of admin) will be about 2 and the C_{max} (at first) is above 10

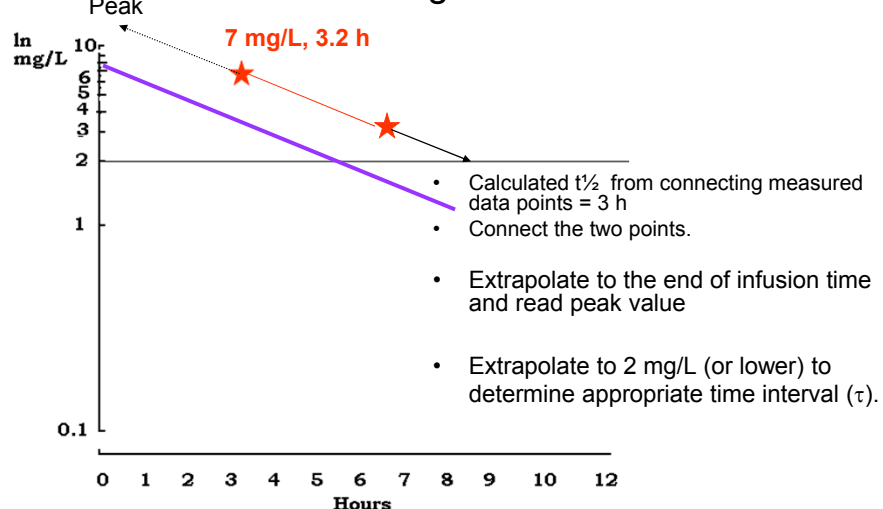
This isn't the desired range, so we can adjust based on the following:

Draw a parallel line and reduce the dose -- use the ratio to determine the dose ... Dose = $100 \times 8/12 = 66.6$ mg

All of this is from one sample from the patient

Where 8 is the desired peak and 12 is initial peak

Dosage adjustment based on more than one known concentrations: A 100 mg dose:



Estimate a dose to get a peak of 8 mg/L

Dose = $100 \times 8/12 = 66.6$ mg
 $\tau = ?$

If you have two points that's even better, ... no need to assume that the $CrCL$ gives us $t_{1/2}$...

half life is different between different people

Other methods:

Dosing based on $t_{1/2}$:

- $\tau = 3 t_{1/2}$ i.e., 75 of the drug is cleared.

Single Daily Dose

- Larger dose
- Post-antibiotic effect
- Saves TDM cost

$$50\% + 50\% \text{ of } 50 + 50\% \text{ of } 25$$

$$50 + 25 + 12.5 = 87.5$$

A Case Report

NOT ON EXAM

RT Foster cases

- DM, a 65 y-old 43 kg, 164 cm female patient
- Admitted Feb 18 for diarrhea, dehydration.
- Subsequently pneumonia was diagnosed.
- Day 12: CLcr, 61 mL/min
- Day 24: Sputum contained E.Coli sensitive to Gent
- Day 34: Started Gent 60 mg iv (LD) and 50 mg iv q8h
- Day 36: Peak, 2.6 mg/L (52 min after start infusion); Trough 1.0 mg/L (7.20 after start).
- Day 39: Gent $\uparrow\uparrow\uparrow$ to 60 mg in q8h; "Peak 2.8 mg/L at 2:05"; "Cmin 1.3 mg/L at 6:13".
- Day 40: "adequate random level 3.3 mg/L at 2.08 and low Cmin of 0.8 mg/L at 7.25"
- Day 48: Gent \uparrow 70 mg iv q8h

- Day 49: Gent ↑ 80 mg iv q8h
- Day 50: Gent ↓ 60 mg iv q8h
- Day 51: Peak 1.7 mg/L at 7:07, “low”.
- Day 53: Peak 3.1 mg/L at 1:30 “low”; trough 1.7 mg/L at 7:18 “low”
- Day 55: Peak 3.2 mg/L at 1:22 “low”
- Day 59, Gent D/C.
- Day 63: CLcr, 20 mL/min
- 25 days of subtherapeutic Gent therapy
- CLcr 61 mL/min (Day 12) → 20 mL/min (Day 63).
- Two CLcr tests; 11 Gent levels; five dosage adjustment; 63 days of hospitalization,

Assignment 10

- Recommend an appropriate gentamicin dosage regimen for a 24-yr-old female patient with 172 cm height and 180 kg body weight who is suffering from a cystitis. She has a serum creatinine concentration of 115 $\mu\text{mol/L}$ and is in a normal hydration state.
- Check if the recommended regimen yields desired peak and trough using the C_{min} and C_{max} equations.

Assignment 11

- Recommend an appropriate tobramycin dosage regimen for a 65-yr-old (45 kg, 164 cm) female patient with creatinine clearance of 32 mL/min. She has pneumonia and her body temperature ranges from 38.5 to 39.2°.