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Therapeutic drug monitoring (TDM)

FIFTH STAGE

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LIST OF CONTENT:

Lab no. one

Problems in basic pharmacokinetics (PK) and pharmacodynamics (PD)

Clearance

It determines the maintenance dose **(MD)** that is required to obtain a given steady-state serum concentration **(Css)**.

$$MD = Css^* CL$$

Example: the therapeutic range for theophylline is 10–20 µg/mL for the treatment of asthma with concentrations of 8–12 µg/mL considered as a reasonable starting point. If it were known that the theophylline clearance for a patient 3 L/h and the desired steady-state theophylline serum concentration was 10 µg/mL.

➢ What is the theophylline maintenance dose to achieve this concentration?

$$MD = Css^* CL$$

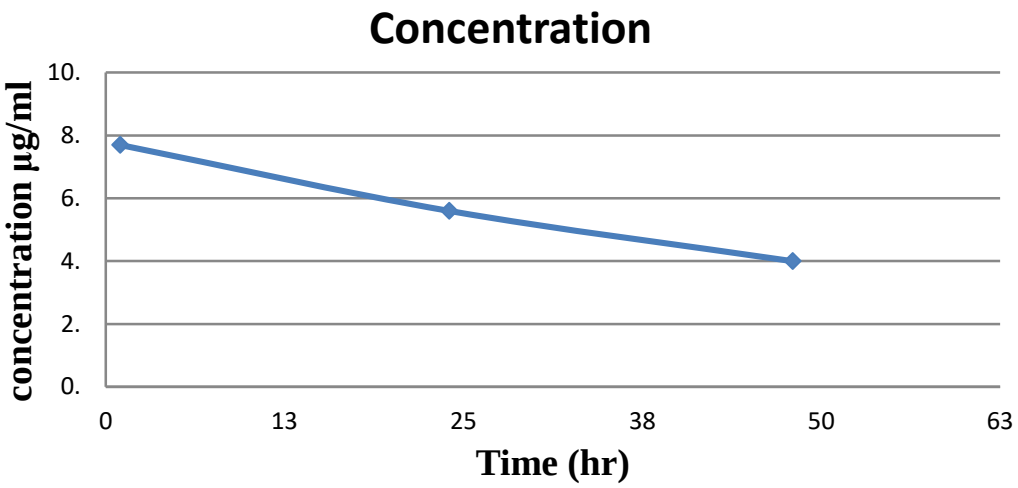
- Therapeutic concentration (Css) = 10 µg/ml
- Converted unit of Css to mg/L
- Css = 10 mg/L
- MD = 10 mg/L · 3 L/h = 30 mg/h

Half-Life and Elimination rate constant

Example: After the first dose of gentamicin is given to a patient with renal failure, the following serum concentrations are obtained:

❑ Compute the half-life and the elimination rate constant for this patient?

Time after dosage administration (hr)	Concentration (µg/ml)
1	7.7
24	5.6
48	4



- Since all of the concentrations fall on the straight line, any two concentration/time pairs can be used to compute the elimination rate constant (ke):
- **ke = −(ln C1 − ln C2)/(t1 − t2).**
- ke =−(ln 7.7 − ln 4)/(1 h − 48 h) = 0.0139 h^{-1}.
- The elimination rate constant can be used to calculate the half-life for the patient:
- **t1/2 = 0.693/ke.**
- t1/2 = 0.693/0.0139 h^{-1} = 50 h.

Bioavailability and Bioequivalence

Example: A new immunosuppressant, Noreject, is being studied in the renal transplant clinic where you work. Based on previous studies, the following area under the serum concentration/ time curves (AUC) were measured after single doses of **10 mg** in renal transplant patients:

- **Intravenous bolus AUC** = 1530 mg · h/L.
- **Oral capsule AUC** = 1220 mg · h/L.
- **Oral liquid AUC** = 1420 mg · h/L.
- What is the bioavailability of the oral capsule and oral liquid?
- What is the relative bioavailability of the oral capsule compared to the oral liquid?
- The bioavailability for the capsule and liquid are:
- **F = AUCPO/AUCIV**
- For capsule, F =(1220 mg · h/L)/(1530 mg · h/L) = 0.80 or 80%.

- For liquid, F = (1420 mg · h/L)/ (1530 mg · h/L) = 0.93 or 93%.
- The relative bioavailability is:
- **Frelative = AUCcapsule/ AUCliquid.**
- Frelative = (1220 mg · h/L)/(1420 mg · h/L) = 0.86 or 86%.

H.W.

After administering a single dose of 100 mg of penicillin

What is the bioavailability of the oral tablet and oral liquid?

What is the relative bioavailability of the oral capsule compared to the oral liquid?

AUC of iv =95 mg.hr/L

AUC oral tablet =85mg.hr/L

AUC oral liquid =70mg.hr/L

Lab no. two

Clinical (PK) Problems in special population

Creatinine Clearance

$$CrCL(ml/min) = \frac{U_{Cr} x V_{urine}}{S_{Cr} x T}$$

- U_{Cr} = the urine creatinine concentration (mg/dl).
- V_{urine} = the volume of urine collected (ml).
- S_{Cr} = the serum creatinine collected at the midpoint of the urine collection (mg/dl).
- T = the time of urine collection (minute)

Example: A 24-hour urine was collected for a patient with the following results: UCr = 55 mg/dl, Vurine = 1000 mL, SCr = 1.0 mg/dl.

- Due to CrCL measure ml/min
- T unit convert from Hour to minute.
- T=24 hr X 60 min/hr = 1440 min.

$$CrCL(ml/min) = \frac{U_{Cr} x V_{urine}}{S_{Cr} x T}$$

= 38 ml/min.

Cockroft and Gault equation

$$CrCl_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCl_{est} = \frac{0.85(140 - age)BW}{72 \cdot S_{Cr}} \text{ for females}$$

- ❑ CrCL est. = estimated creatinine clearance (ml/min).
- ❑ Age in years.
- ➢ This equation should be used only in patients:
- ✓ Age ≥ 18 y.
- ✓ With the weight of 30% of IBW
- ▪ IBW males (kg) = 50 + 2.3 (Ht – 60)
- ▪ IBW females (kg) = 45 + 2.3 (Ht – 60)
- ▪ Ht: height in inches
- ✓ If Scr values were not stable the Cockroft and Gault equation cannot be used

Example: A 55-year-old, 80-kg, 5-ft 11-in male has a serum creatinine equal to 1.9 mg/dl. The estimated creatinine clearance would be:

Solution

1 ft = 12 in

- IBW males (kg) = 50 + 2.3 (Ht – 60).
- Ht unit in ft and in convert into in.
- Ht= 5X 12 + 11 = 71
- IBW males = 50 + 2.3(71 − 60) = 75 kg.
- So the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used

$$CrCl_{est} = \frac{(140 - 55y)80kg}{72 \cdot 1.9mg/dl}$$

$CrCl_{est}$ = 50 ml/min.

Salazar and Corcoran Equation

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

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

- ❑ Wt = weight (kg).
- ❑ Ht = height (m)
- ❑ Scr = serum creatinine (mg/dl).

1 in = 2.54 cm

- ➢ Its used for obese patient.

Example: A 66-year-old, 120-kg, 5-ft 2-in tall female has a serum creatinine equal to 3.1 mg/dL.
Compute an estimated creatinine clearance for this patient.

Solution

- ✓ This patient is obese, so the Salazar-Corcoran method is used:
- ✓ Height is converted from inches to meters

- ✓ Ht = (62 in · 2.54 cm/in) / (100 cm/m) = 1.57 m.

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

Solution

$$CrCl_{est(females)} = \frac{(146 - 66y)[(0.287 \cdot 120kg) + (9.74 \cdot \{1.57\ m\}^2)]}{60 \cdot 3.1\ mg/dl}$$

$$CrCl_{est} = 25\ ml/min.$$

Renal function

- Estimation of renal function

$$RF = \frac{CL_{Cr}(d)}{CL_{Cr}(t)}$$

- ✓ CL_{Cr} (d) = creatinine clearance in the patient with renal dysfunction
- ✓ CL_{Cr} (t) = creatinine clearance in the typical 55 year-old and 70 kg patient
- ✓ RF = renal function

Maintenance dose:

$$\left(MD/\tau\right)_{(d)} = RF \cdot \left(MD/\tau\right)_{(t)}$$

- Adjustment may be made by reducing the frequency of administration, or reducing the MD or both.
- τ= dosing interval

Example: Adjustment of dose of Amikacin sulfate for 23 year-old, 68 kg patient with CLCr 13 mL/min.

Usual dose regimen: 7.5 mg/kg I.M. every 12 hrs

CLCr expected for typical patient = 77 mL/min

- RF (d) = 13/77 = 0.17.
- MD Amikacin has to be reduced by a factor of 6 (or 1/0.17).
- Thus, the maintenance regimen could be:
- Dosing interval= 6 X 12 = 72 hrs.
- The regimen: 500 mg (7.5 mg/kg x 68 kg) every 72 hrs.

2. MD may be reduced by a factor of 6

✓ MD = 500 mg/6 = 83 mg

✓ The regimen: 83 mg every 12 hrs.

3. Both dosing interval and MD may be adjusted to reduce average dosing.

✓ The regimen: 167 mg every 24 hrs.

Measurement of liver function

- ❑ No single laboratory test to assess the liver function (not like $CLCr_{est}$ to measure renal function).
- ❑ The most common way to estimate the ability of the liver to metabolize the drug is to determine the ***Child-Pugh score*** for a patient.

Test/symptom	Score 1 point	Score 2 points	Score 3 points
Total bilirubin (mg/dl)	< 2.0	2.0 – 3.0	>3.0
Serum albumin (g/dl)	> 3.5	2.8 – 3.5	< 2.8
Prothrombin time (seconds prolonged over control)	< 4	4 – 6	> 6
Ascites	Absent	Slight	Moderate
Hepatic encephalopathy	None	Moderate	Severe

Dosage adjustment

- ❑ A Child-Pugh score of 8 – 9 : a moderate decrease (± 25%) in initial daily drug dose for agents that are primarily (≥ 60%) metabolized hepatically.
- ❑ A Child-Pugh score of ≥ 10 : a significant decrease in initial daily dose (± 50%) is required for drugs that are mostly liver metabolized.
- ❑ It is possible to:
- ✓ Decrease the dose while retaining the normal dosage interval.
- ✓ Retain the usual dose and prolong the dosage interval.
- ✓ Modify both the dose and dosage interval.

Example: A 62-year-old, 65-kg male with hepatic cirrhosis

- ✓ Total bilirubin = 2.6 mg/dL
- ✓ Serum albumin = 2.5 mg/dL.
- ✓ Prothrombin time prolonged over normal by 8 seconds.
- ✓ Slight amount of ascitic fluid.
- ✓ No hepatic encephalopathy.

Compute the patient's Child- Pugh score.

1. Child-Pugh score (from Table):

- ✓ Total bilirubin = 2 points.
- ✓ albumin = 3 points.
- ✓ Prothrombin time = 3 points.
- ✓ Ascites = 2 points.
- ✓ Encephalopathy= 1 point.
- ❑ Total = 2+3+3+2+1=11 points (severe hepatic dysfunction).

H.W.

A 70-year-old, 60-kg male with hepatic cirrhosis

- ✓ Total bilirubin = 3 mg/dL
- ✓ Serum albumin = 3 mg/dL.
- ✓ Prothrombin time prolonged over normal by 4 seconds.
- ✓ Slight amount of ascitic fluid.
- ✓ No hepatic encephalopathy.

Compute the patient's Child- Pugh score.

Lab no. three

Problems in clinical (PK) for antibiotics

(Aminoglycosides and Vancomycin)

Example: 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 the creatinine clearance:

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

$$CrCl_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCl_{est} = \frac{(140 - 50y)70kg}{72 \cdot 0.9mg/dL} = 97 \text{ mL/min}$$

2. Estimate $t_{1/2}$:

✓ $K_e = 0.298\ h^{-1}$

✓ **$t_{1/2} = 0.693/ K_e$**

✓ $t_{1/2} = 0.693/0.298\ h^{-1} = 2.3$ h

3. Estimate volume of distribution:

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 (70 kg) = 18.2 L.

4. Choose desired steady-state serum concentrations:

❑ G -ve pneumonia patients treated with aminoglycoside antibiotics require steady-state peak concentrations (Css_{max}) equal to 8–10 µg/mL.

❑ Steady-state trough (Css_{min}) concentrations should be <2 µg/mL to avoid toxicity.

❑ Set $Css_{max} = 9$ µg/mL and $Css_{min} = 1$ µg/mL.

5. Use intermittent intravenous infusion equations to compute dose:

❑ Calculate required dosage interval (τ) using a 1-hour infusion:

✓ **$\tau = (\ln Css_{max} - \ln Css_{min}) / k_e + t'$**

✓ $\tau = [(\ln 9\ \mu g/mL - \ln 1\ \mu g/mL) / 0.298\ h^{-1}] + 1\ h = 8.4\ h$

➢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, whenever possible.

➢In this case, the dosage interval would be rounded to 8 hours.

➢Steady-state peak concentrations are similar if drawn immediately after a 1-hour infusion or 1/2 hour after a 1/2-hour infusion

❑ The dose could be administered either way:

✓ **$K0 = Cssmax.ke .V[(1 - e{-}ke\tau) / (1 - e{-}ket')]$**

✓ μg/mL = mg/L and this concentration unit was substituted for Css_{max}.

✓ $K0 = (9\ mg/L \cdot 0.298\ h{-}1 \cdot 18.2\ L)\{[1 - e{-}(0.298\ h{-}1)(8\ h)] / [1 - e{-}(0.298\ h{-}1)(1\ h)]\}$

✓ $K_0 = 172\ mg$

➢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:

❑ Loading doses should be considered for patients with CrCL<60 mL/min.

❑ As noted, this patient has good renal function (CrCL ≥ 60 mL/min) so a loading dose wouldn't be prescribed for this patient.

Example: JM is a 50-year-old, 70-kg (5 ft 10 in) male with a methicillin-resistant *S. aureus* (MRSA) wound infection. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute a **Vancomycin** dose for this patient.

1. Estimate the creatinine clearance:

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

$$CrCl_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCl_{est} = \frac{(140 - 50y)70kg}{72 \cdot 0.9mg/dL} = 97 \text{ mL/min}$$

2. Estimate Vancomycin clearance:

❑ The Vancomycin clearance versus creatinine clearance relationship is used to estimate the Vancomycin clearance for this patient:

❑ Cl = 0.695(CrCl) + 0.05

❑ Cl = 0.695[(97 mL/min)/70kg] + 0.05 = 1.015 mL/min/kg

3. Estimate Vancomycin volume of distribution:

❑ The average volume of distribution for Vancomycin is 0.7 L/kg:

❑ V = 0.7 L/kg•70 kg = 49 L.

4. Estimate Vancomycin K_e and $t_{1/2}$:

- ❑ **$K_e = CL/V$**
- ❑ K_e = (1.015 mL/min/kg •60 min/h) / (0.7 L/kg •1000 mL/L)
- ❑ $K_e = 0.087\ h^{-1}$
- ❑ **$t_{1/2} = 0.693 / K_e$**
- ❑ $t_{1/2} = 0.693 / 0.087\ h^{-1}$
- ❑ t1/2 = 8 h

5. Choose desired steady-state serum concentrations:

- ❑ Patients with *S. aureus* wound infections need to be carefully assessed.
- ❑ This patient did not appear to be in acute distress, with a normal temperature and slightly elevated white blood cell count (WBC). The wound was warm and red with a slight amount of purulent discharge.
- ❑ Because the infection was localized to the wound area, a **Css_{min}** = 7 µg/mL and **Css_{max}** = 20 µg/mL were chosen.

6. Use intravenous bolus equations to compute dose:

Calculate required dosage interval (τ):

- ✓ **$\tau = (\ln Css_{max} - \ln Css_{min}) / K_e$**
- ✓ τ = (ln 20 µg/mL − ln 7 µg/mL) / 0.087 h–1 = 12.1 h.

➢Dosage intervals should be rounded to clinically acceptable intervals of 12 hours, 18 hours, 24 hours, 36 hours, 48 hours, 72 hours, and multiples of 24 hours thereafter, whenever possible.

➢In this case, the dosage interval would be rounded to 12 hours.

Calculate required dose (D):

- ✓ **$D = Css_{max}\, V(1 - e^{-ke\tau})$**
- ✓ µg/mL = mg/L and this concentration unit was substituted for Css_{max}.
- ✓ D = 20 mg/L •49 L [1 − e− (0.087 h–1) (12 h)]= 635 mg

➢Vancomycin doses should be rounded to the nearest 100–250 mg.

➢This dose would be rounded to 750 mg.

➢The prescribed maintenance dose would be 750 mg every 12 hours.

7. Compute loading dose (LD), if needed:

- ❑ Loading doses should be considered for patients with CrCL<60 mL/min.
- ❑ As noted, this patient has good renal function (CrCL ≥ 60 mL/min) so a loading dose wouldn't be prescribed for this patient.

Lab no. four

Problems in clinical PK/PD for cardiovascular agents

(Digoxin, Lidocain, Procainamide)

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. Compute an intravenous **digoxin** dose for this patient to control ventricular rate.

1. Estimate the creatinine clearance:

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

$$CrCL_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCL_{est} = \frac{(140 - 50y)70kg}{72 \cdot 0.9mg/dL} = 97$$

2. Estimate the Digoxin clearance:

❑ The drug clearance versus CrCL relationship is used to estimate the Digoxin CL for this patient (CL NR = 40 mL/min since the patient does not have moderate to severe heart failure):

❑ NOTE: CL NR is digoxin non-renal clearance.

✓ **CL = 1.303 (CrCL) + CL NR**

✓ CL = 1.303(97 ml/min) + 40 ml/min = 167 ml/min

3. Estimate volume of distribution:

➢The patient has good renal function and is non-obese.

➢Therefore, a volume of distribution equal to 7 L/kg:

❑ V = 7 L/kg•70 kg = 490 L

4. Choose desired steady-state serum concentrations:

❑ For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/ml.

❑ A serum concentration equal to 1.2 ng/ml will be chosen for this patient

5. Calculate maintenance dose (D/τ):

✓ IV digoxin will be used (F = 1).

✓ **F** is the bioavailability fraction for the oral dosage form (F = 1 for intravenous digoxin)

✓ **Note:** For concentration units **ng/ml = µg/L**.

✓ Conversion factors are needed to change milliliters to liters (**1000 ml/L**) and minutes to days (**1440 min/d**).

✓ CL = 167 ml/min . 1440 min/d / 1000 ml/L = 240.48 L/d.

❑ **D/τ = (Css•Cl) / F**

❑ D/τ = (1.2 µg/L .240.48 L/d) / 1 = 288 µg/d, round to 250 µg/d

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

✓ IV loading dose (F = 1) could be used in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used and concentrations allowed to accumulate over 3–5 half-lives.

❑ **LD = (Css•V) / F**

❑ LD = (1.2 µg/L •490 L) / 1 = 588 µg rounded to 500 µg

✓ In this case, an initial intravenous dose of 250 µg would be given initially, followed by two additional intravenous doses of 125 µg each.

✓ One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 3.5 mg/dL indicating **renal impairment**, and it has been stable over the last 5 days since admission. Compute an intravenous digoxin dose for this patient to control ventricular rate.

1. Estimate the creatinine clearance:

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

$$CrCL_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCL_{est} = \frac{(140 - 50y)70kg}{72 \cdot 3.5mg/dL} = 25mL/min$$

2. Estimate the Digoxin clearance:

❑ The drug clearance versus CrCL relationship is used to estimate the Digoxin CL for this patient (CL NR = 40 mL/min since the patient does not have moderate to severe heart failure):

✓ **CL = 1.303 (CrCL) + CL NR**

✓ CL = 1.303(25 ml/min) + 40 ml/min = 73 ml/min

3. Estimate volume of distribution:

✓ The patient has poor renal function and is non-obese.

✓ Therefore, the volume of distribution equation that adjusts the parameter estimate for renal dysfunction is:

❑ $\mathbf{V = \{226 + \frac{298 * CrCL}{29.1 + CrCL}) \{Wt/70)}$

❑ **V**

$$= \{226 + \frac{298 * 25 \text{ ml/min}}{29.1 + 25 \text{ ml/min}}\} (70 \text{ kg}/70) = 364 \text{ L}$$

4. Choose desired steady-state serum concentrations:

❑ For a patient with atrial fibrillation, the desired digoxin concentration would be 0.8–1.5 ng/ml.
❑ A serum concentration equal to 1.2 ng/ml will be chosen for this patient

5. Calculate maintenance dose (D/τ):

✓ IV digoxin will be used (F = 1).

✓ **Note:** For concentration units **ng/ml = µg/L**.

✓ Conversion factors are needed to change milliliters to liters (**1000 ml/L**) and minutes to days (**1440 min/d**).

✓ CL = 73 ml/min . 1440 min/d / 1000 ml/L = 105.12 L/d.

❑ **D/τ = (Css •Cl) / F**
❑ D/τ = (1.2 µg/L .105.12 L/d) / 1 = 126 µg/d, round to 125 µg/d

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

✓ IV loading dose (F = 1) could be used in this patient to achieve the desired pharmacologic effect quicker than would occur if maintenance doses alone were used and concentrations allowed to accumulate over 3–5 half-lives.

❑ **LD = (Css•V) / F**
❑ LD = (1.2 µg/L •364 L) / 1 = 437 µg rounded to 400 µg

✓ In this case, an initial intravenous dose of 200 µg would be given initially, followed by two additional intravenous doses of 100 µg each.

✓ One of the loading doses could be withheld if pulse rate was less than 50–60 beats per minute or other undesirable digoxin adverse effects were noted.

Example1: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with atrial fibrillation for less than 24 hours. His current serum creatinine is 0.9 mg/dL, and it has been stable over the last 5 days since admission. A Digoxin tablet dose of 250 µg/day was prescribed and expected to achieve steady-state serum concentration equal to 0.8 µg/L. After a week of treatment, a steady-state serum concentration was measured and was equal to 0.6 µg/L. Calculate a new digoxin tablet dose that will provide a steady-state serum concentration equal to 0.9 µg/L.

1. Estimate the creatinine clearance:

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

$$CrCL_{est} = \frac{(140 - age)BW}{72 \cdot S_{Cr}} \text{ for males}$$

$$CrCL_{est} = \frac{(140 - 50y)70kg}{72 \cdot 0.9mg/dL} = 9\,mL/$$

2. Compute new dose to achieve desired serum concentration:

D new = (Css new / Css old) D old

❑ **D_{new}** = (0.9 ng/mL / 0.6 ng/mL) 250 µg/d = 375 µg/d.

❑ The new suggested dose would be 375 µg/d given as digoxin tablets to be started at the next scheduled dosing time.

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with intravenous lidocaine. He has normal liver and cardiac function. Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 3 μg/ml.

1. Estimate half-life and elimination rate constant:

- The expected lidocaine half-life (t1/2) is 1.5 hours.
- $\mathbf{k_e = 0.693/t_{1/2}}$
- $\mathbf{k_e}$ = 0.693 / 1.5 hrs = 0.462 hrs^{-1}

2. Estimate V and CL:

- The patient is not obese, so the estimated lidocaine **Vc** and **Varea** will be based on actual body weight:
  - BMI = 25 for IBW
  - BMI = Wt / Ht^2

Vc = 0.5 L/kg •75 kg = 38 L

Varea = 1.5 L/kg •75 kg = 113 L

$CL = k_e$. Varea

CL = 0.462 hrs^{-1} •113 L = 52.2 L/hrs.

3. Compute dosage regimen:

- Therapy will be started by administering an intravenous loading dose of lidocaine to the patient:

LD = (Css•Vc)
LD = 3 mg/L•38 L = 114 mg, rounded to 100 mg IV over 2–4 minutes.

- An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

- A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered:

- ✓ **K_0 =Css •CL**
- ✓ Converted unit of CL via divided by 60 min/hrs.
- ✓ CL = 52.2 L/hrs / 60 min/hrs = 0.87 L/min.
- ✓ **K_0 =** (3 mg/L •0.87 L/min) = 2.6 mg/min, rounded to 2.5 mg/min.

Example: OI is a 60-year-old, 85-kg (6 ft 1 in) male with ventricular fibrillation who requires therapy with intravenous lidocaine. He has liver cirrhosis (Child-Pugh score = 11). Suggest an initial intravenous lidocaine dosage regimen designed to achieve a steady-state lidocaine concentration equal to 4 μg/ml.

1. Estimate half-life and elimination rate constant:

- ❑ The expected lidocaine half-life (t1/2) is 5 hrs.
- ❑ $\mathbf{k_e = 0.693/t_{1/2}}$
- ❑ $\mathbf{k_e}$ = 0.693 / 5 hrs = 0.139 hrs^{-1}

2. Estimate V and CL:

❑ The patient is not obese, so the estimated lidocaine **Vc** and **Varea** will be based on actual body weight:

Vc = 0.6 L/kg •85 kg = 51 L

Varea = 2.6 L/kg •85 kg = 221 L

CL = k_e . Varea

CL = 0.139 hrs^{-1}•221 L = 31 L/hrs.

3. Compute dosage regimen:

❑ Therapy will be started by administering an intravenous loading dose of lidocaine to he patient:

- ✓ **LD = (Css•Vc)**
- ✓ **LD** = 4 mg/L•51 L = 204 mg, rounded to 200 mg IV over 4–8 minutes.

❑ An additional dose equal to 50% of the loading dose can be given if arrhythmias recur 20–30 minutes after the initial loading dose.

❑ A lidocaine continuous intravenous infusion will be started immediately after the loading dose has been administered:

- ✓ **K_0 =Css•CL**
- ✓ Converted unit of CL via divided by 60 min/hrs.
- ✓ CL = 31 L/hrs / 60 min/hrs = 0.517 L/min.
- ✓ **K_0 =** (4 mg/L•0.527 L/min) = 2.1 mg/min, rounded to 2 mg/min.

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male with ventricular tachycardia who requires therapy with oral procainamide sustained-release tablets. He has normal liver and cardiac function. Suggest an initial oral procainamide dosage regimen designed to achieve a steady-state procainamide concentration equal to 4 μg/ml.

1. Estimate half-life and elimination rate constant:

❑ The expected lidocaine half-life (t1/2) is 3.3 hrs.

❑ $\mathbf{k_e = 0.693/t_{1/2}}$

❑ $\mathbf{k_e}$ = 0.693 / 3.3 hrs = 0.210 hrs^{-1}

2. Estimate V and CL:

❑ The patient is not obese, so the estimated lidocaine **V** will be based on actual body weight:

✓ **V** = 2.7 L/kg •75 kg = 203 L

❑ $\mathbf{CL = k_e . V}$

❑ **CL** = 0.21 hrs^{-1}•203 L = 42.6 L/hrs.

3. Compute dosage regimen:

❑Oral sustained-release procainamide tablets will be prescribed to this patient (F = 0.83).

❑Because the patient has a rapid procainamide clearance and short half-life, the initial dosage interval (τ) will be set to 6 hrs:

✓ $\mathbf{D = (Css * CL* \tau) / F}$

✓ D = (4 mg/L•42.6 L/hrs•6 hrs) / 0.83 = 1231 mg, rounded to 1250 mg every 6 hours.

❑Oral sustained-release procainamide tablets will be prescribed every 6 hrs or every 12 hrs according patient state.

Lab no. five

Problems in clinical PK/PD for anticonvulsant agents

(phenytoin, carbamazepine, Valproic acid, phenobarbiton, ethosuxsimide)

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. Suggest an initial carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration equal to 6–8 µg/ml.

Estimate carbamazepine dose

❑ The suggested initial dosage rate for immediate-release carbamazepine tablets in an adult patient is 200 mg twice daily (400 mg/d).

❑ This dose would be titrated upward in 200-mg increments every 2–3 weeks while monitoring for adverse and therapeutic effects.

❑ The goal of therapy includes maximal suppression of seizures, avoidance of side effects, and a target drug range of 800–1200 mg/d.

❑ A steady-state trough total carbamazepine serum concentration should be measured after steady state is achieved in 2–3 weeks at the highest dosage rate attained.

❑ Carbamazepine serum concentrations should also be measured if the patient experiences an exacerbation of their epilepsy, or if the patient develops potential signs or symptoms of carbamazepine toxicity.

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral carbamazepine. He has normal liver function. After dosage titration, the patient was prescribed 200 mg in the morning, 200 mg in the afternoon, and 400 mg at bedtime (800 mg/d) of carbamazepine tablets for 1 month, and the steady-state carbamazepine total concentration equals 3.8 µg/ml. The patient is assessed to be compliant with his dosage regimen. Suggest a carbamazepine dosage regimen designed to achieve a steady-state carbamazepine concentration within the therapeutic range.

Use pseudo linear pharmacokinetics to predict new concentration for a dosage increase:

- Since the patient is receiving carbamazepine tablets, a convenient dosage change would be 200 mg/d and an increase to 1000 mg/d (400 mg in the morning and bedtime, 200 mg in the afternoon) is suggested.
- **Css new = (D new / D old)Css old**
- **Css $_{new}$** =(1000 mg/d / 800 mg/d) 3.8 µg/ml = 4.8 µg/ml.

Then compute 10–20% factor to account for autoinduction pharmacokinetics:

- Because of autoinduction pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics:
- Css = 4.8 µg/ml · 0.90 = 4.3 µg/ml and Css = 4.8 µg/ml · 0.80 = 3.8 µg/ml.
- Thus, a dosage increase of 200 mg/d would be expected to yield a total carbamazepine steady-state serum concentration between 3.8 and 4.3 µg/ml.

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonicclonic seizures who requires therapy with oral Valproic acid. He has normal liver function and takes no medications that induce hepatic enzymes. Suggest an initial Valproic acid dosage regimen designed to achieve a steady-state Valproic acid concentration equal to 50 µg/ml.

1. Estimate the Valproic acid clearance and volume of distribution:

❑ These parameters estimated according to disease states and conditions present in the patient:

✓ The CL for an adult patient not taking other drugs that induce hepatic drug metabolism is 10 ml/h/kg.

✓ CL = 75 kg · 10 ml/h/kg = 750 ml/h or 0.75 L/h.

✓ The V for an adult patient is 0.15 L/kg. ✓ V = 75 kg · 0.15 L/kg = 11 L

2. Estimate $t_{1/2}$ and K_e:

✓ **$t_{1/2}$ = (0.693 · V) / CL**

✓ **$t_{1/2}$** = (0.693 · 11 L) / 0.75 L/h = 10 h

✓ **K_e = CL / V**

✓ **K_e** = 0.75 L/h / 11L = 0.069 h-1.

3. Compute dosage regimen:

➢ Oral enteric-coated divalproex sodium tablets will be prescribed to this patient (F = 1).

➢ Note: µg/ml = mg/L

➢ The dosage equation for oral Valproic acid is:

✓ **D = (Css · CL · τ) / F**

✓ D = (50 mg/L· 0.75 L/h · 12 h) / 1 = 450 mg, rounded to 500 every 12 hours.

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonicclonic seizures who requires therapy with oral Valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets (1000 mg/d) for 1 month, and the steady-state Valproic acid total concentration equals 38 µg/ml. The patient is assessed to be compliant with his dosage regimen. Suggest a Valproic acid dosage regimen designed to achieve a steady-state Valproic acid concentration of 80 µg/ml.

Use pseudo linear pharmacokinetics to predict new concentration for a dosage increase:

- **D new = (Css new / Css old) D old**
- **D_{old}** = (80 µg/ml / 38 µg/ml) 1000 mg/d = 2105 mg/d, rounded to 2000 mg/d or 1000 mg every 12 hours.

Then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics:

- Because of this pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics:
- Css = 80 µg/ml · 0.90 = 72 µg/ml and Css = 80 µg/ml · 0.80 = 64 µg/ml.
- Thus, a dosage rate of 2000 mg/d would be expected to yield a total Valproic acid steady-state serum concentration between 64 –72 µg/ml.

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonicclonic seizures who requires therapy with oral Valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets (1000 mg/d) for 1 month, and the steady-state Valproic acid total concentration equals 38 µg/ml. The patient is assessed to be compliant with his dosage regimen. Suggest a Valproic acid dosage regimen designed to achieve a steady-state Valproic acid concentration of 80 µg/ml.

1. Compute pharmacokinetic parameters:

❑ Valproic acid CL can be computed using a steady-state Valproic acid concentration:

❑ Note: µg/ml = mg/L

❑ **CL = [F(D/τ)] / Css**

❑ CL = [1(500 mg/12 h)] / (38 mg/L) = 1.1 L/h.

2. Compute Valproic acid dose:

❑ Valproic acid clearance is used to compute the new dose:

❑ **D = (Css · CL · τ) / F**

❑ **D** = (80 mg/L · 1.1 L/h · 12 h) / 1 = 1056 mg, rounded to 1000 mg every 12 hours.

❑ Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics:

❑ Css = 80 µg/ml · 0.90 = 72 µg/ml and Css = 80 µg/ml · 0.80 = 64 µg/ ml.

❑ Thus, a dosage rate of 2000 mg/d would be expected to yield a total Valproic acid steady-state serum concentration between 64–72 µg/ml.

Example: GO is a 50-year-old, 75-kg (5 ft 10 in) male with tonicclonic seizures who requires therapy with oral phenobarbital. He has normal liver and renal function. Suggest an initial phenobarbital dosage regimen designed to achieve a steady-state concentration equal to 20 µg/ml.

1-Estimate clearance and volume of distribution according to disease states and conditions present in the patient:

- ❑ The phenobarbital CL for an older patient is 4 mL/h/kg.
- ❑ CL= 75 kg · 4 mL/h/kg = 300 mL/h or 0.3 L/h.
- ❑ The estimated V would be:
- ❑ V= 75 kg · 0.7 L/kg = 53 L.

2-Estimate $t_{1/2}$ and K_e:

- ✓ **$t_{1/2}$ = (0.693 · V) / CL**
- ✓ **$t_{1/2}$** = (0.693 · 53 L) / 0.3 L/h = 122 h
- ✓ **K_e = CL / V**
- ✓ **K_e** = 0.3 L/h / 53L = 0.0057 h−1

3. Compute dosage regimen:

- ➢ Oral phenobarbital tablets will be prescribed to this patient (F = 1).
- ➢ Note: µg/ml = mg/L
- ➢ The dosage equation for oral phenobarbital is:
- ✓ **D = (Css · CL · τ) / F**
- ✓ D = (20 mg/L· 0.3 L/h · 24 h) / 1 = 144 mg, rounded to 120 every 24 hours.

Example: LK is a 13-year-old, 47-kg (5 ft 1 in) female with complex partial seizures who requires therapy with oral primidone. After dosage titration, the patient was prescribed 250 mg every 8 hours of Primidone tablets (750 mg/d) for 1 month, and the steady-state Primidone and Phenobarbital steady-state concentrations equal 3 µg/ml and 15 µg/ml, respectively. The patient is assessed to be compliant with her dosage regimen. Suggest a primidone dosage regimen designed to achieve a steady-state primidone concentration of 6 µg/ml.

1. Compute a new dose to achieve desired serum concentration:

➢ **Use linear pharmacokinetics to predict new dose:**

❑ **D new = (Css new / Css old) D old**

❑ **D_{new}** = (6 µg/mL / 3 µg/mL) 750 mg/d = 1500 mg/d, or 500 mg every 8 hours.

➢ The dosage regimen would be titrated to this value over a period of 1–2 weeks to avoid adverse effects.

➢ Use linear pharmacokinetics, the resulting steady-state phenobarbital serum concentration would equal :

✓ **Css new = (D new / D old) Css old**

✓ **Css_{new}** = (1500 mg/d / 750 mg/d) 15 µg/ml = 30 µg/ml.

Example: LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral Ethosuximide. She has normal liver and renal function. Suggest an initial Ethosuximide dosage regimen designed to achieve a steady-state Ethosuximide concentration equal to 50 µg/ml.

1. Estimate the Ethosuximide clearance and volume of distribution:

❑ These parameters estimated according to disease states and conditions present in the patient:

✓ The CL for an older patient is 12 ml/h/kg.

✓ CL = 47kg · 12 ml/h/kg = 564 ml/h or 0.564 L/h.

✓ The V for an adult patient is 0.7 L/kg. ✓ V = 47 kg · 0.7 L/kg = 33 L

2. Estimate $t_{1/2}$ and K_e:

✓ **$t_{1/2}$ = (0.693 · V) / CL**

✓ **$t_{1/2}$** = (0.693 · 33 L) / 0.564 L/h = 41 h

✓ **K_e = CL / V**

✓ **K_e** = 0.564 L/h / 33L = 0.017 h-1

3. Compute dosage regimen:

➢ Oral Ethosuximide capsules will be prescribed to this patient (F = 1).

➢ Note: µg/ml = mg/L

➢ The dosage equation for Oral Ethosuximide capsules is:

✓ **D = (Css · CL · τ) / F**

✓ D = (50 mg/L · 0.564 L/h · 12 h) / 1 = 338 mg, rounded to 250 every 12 hours.

Example: LK is a 13-year-old, 47-kg (5 ft 1 in) female with absence seizures who requires therapy with oral Ethosuximide. After dosage titration, the patient was prescribed 500 mg every 12 hours of Ethosuximide capsules (1000 mg/d) for 1 month, and the steady-state Ethosuximide total concentration equals 38 µg/ml. The patient is assessed to be compliant with her dosage regimen. Suggest an Ethosuximide dosage regimen designed to achieve a steady-state Ethosuximide concentration of 80 µg/ml.

➢ **Use pseudo linear pharmacokinetics to predict new concentration for a dosage increase:**

❑ **Css new = (D new / D old)Css old**

❑ **Css $_{new}$** = (80 µg/ml / 38 µg/ml) 1000 mg/d = 2105 mg/d, rounded to 2000 mg/d or 1000 mg every 12 hours.

➢ **Then compute 10–20% factor to account for nonlinear, concentration-dependent plasma protein binding pharmacokinetics:**

❑ Because of this pharmacokinetics, the serum concentration would be expected to increase 10% less, or 0.90 times, to 20%, or 0.80 times, less than that predicted by linear pharmacokinetics:

❑ Css = 80 µg/ml · 0.90 = 72 µg/ml and Css = 80 µg/ml · 0.80 = 64 µg/ml.

❑ Thus, a dosage rate of 2000 mg/d would be expected to yield a total Valproic acid steady-state serum concentration between 64 –72 µg/ml.

Example: KL is a 51-year-old, 75-kg (5 ft 10 in) male with tonicclonic seizures who requires therapy with oral Valproic acid. After dosage titration, the patient was prescribed 500 mg every 12 hours of enteric-coated divalproex sodium tablets (1000 mg/d) for 1 month, and the steady-state Valproic acid total concentration equals 38 µg/ml. The patient is assessed to be compliant with his dosage regimen. Suggest a Valproic acid dosage regimen designed to achieve a steady-state Valproic acid concentration of 80 µg/ml.

1. Compute pharmacokinetic parameters:

❑ Valproic acid CL can be computed using a steady-state Valproic acid concentration:

❑ Note: µg/ml = mg/L

❑ **CL = [F(D/τ)] / Css**

❑ CL = [1(500 mg/12 h)] / (38 mg/L) = 1.1 L/h.

2. Compute Valproic acid dose:

❑ Valproic acid clearance is used to compute the new dose:

❑ **D = (Css · CL · τ) / F**

❑ **D** = (80 mg/L · 1.1 L/h · 12 h) / 1 = 1056 mg, rounded to 1000 mg every 12 hours.

❑ Because of nonlinear, concentration-dependent protein binding pharmacokinetics, the total steady-state serum concentration would be expected to be 10% less, or 0.90 times, to 20% less, or 0.80 times, than that predicted by linear pharmacokinetics:

❑ Css = 80 µg/ml · 0.90 = 72 µg/ml and Css = 80 µg/ml · 0.80 = 64 µg/ ml.

❑ Thus, a dosage rate of 2000 mg/d would be expected to yield a total Valproic acid steady-state serum concentration between 64–72 µg/ml.

3-Compute a new dose to achieve desired serum concentration:

➢ **Use linear pharmacokinetics to predict new dose:**

❑ **D new = (Css new / Css old) D old**

❑ **D_{new} =** (80 µg/mL / 38 µg/mL) 1000 mg/d = 2105 mg/d, rounded to 2000 mg/d or 1000 mg every 12 hours.

Example: JM is an epileptic patient being treated with phenytoin. He has hypoalbuminemia (albumin = 2.2 g/dL) and normal renal function (CrCL = 90 mL/min). His total phenytoin concentration is 7.5 µg/ml. Assuming that any unbound concentrations performed by the clinical laboratory will be conducted at 25°C, compute an estimated normalized phenytoin concentration for this patient.

Estimate normalized total phenytoin concentration:

- ❑ C_{Normal} **Binding = C/(X · Alb + 0.1)**
- ❑ C_{Normal} **Binding** = (7.5 µg/mL) / (0.25 · 2.2 g/dl + 0.1) = 11.5 µg/ml.
- ❑ **Cf EST = 0.1 CNormal Binding**
- ❑ $C_{f\ EST}$ = 0.1 · 11.5 µg/mL = 1.2 µg/m.

❑ This patient's estimated normalized total phenytoin concentration is expected to provide an unbound concentration equivalent to a total phenytoin concentration of 11.5 µg/mL for a patient with normal drug protein binding (C_f **EST** = 1.2 µg/mL).

❑ Because the estimated total value is within the therapeutic range of 10–20 µg/mL, it is likely that the patient has an unbound phenytoin concentration within the therapeutic range.

Example: TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. Suggest an initial Phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration equal to 12 µg/ml.

1. Estimate Michaelis-Menten constants:

❑ These parameters estimated according to disease states and conditions present in the patient.

❑ The V_{max} for a nonobese (75-kg) adult patient with normal liver and renal function is 7 mg/kg/d.

➢ V_{max} = 7 mg/kg/d · 75 kg = 525 mg/d.

❑ K_m = 4 mg/L.

2. Compute dosage regimen:

❑ Oral extended phenytoin sodium capsules will be prescribed to this patient (F = 1, S = 0.92).

❑ The initial dosage interval (τ) will be set to 24 hours.

❑ Note: µg/mL = mg/L

❑ The dosage equation for phenytoin is:

$$MD = \frac{Vmax.\ Css}{S(Km+Css)}$$

$$MD = \frac{525^{mg/d} \cdot 12^{mg/L}}{0.92(4mg/L + 12\ mg/L)}$$

= 428 mg/d, rounded to 400 mg/d.

Example: TD is a 50-year-old, 75-kg (5 ft 10 in) male with simple partial seizures who requires therapy with oral phenytoin. He has normal liver and renal function. The patient was prescribed 400 mg/d of extended phenytoin sodium capsules for 1 month, and the steady-state phenytoin total concentration equals 6.2 µg/ ml. The patient is assessed to be compliant with his dosage regimen. Suggest an initial phenytoin dosage regimen designed to achieve a steady-state phenytoin concentration within the therapeutic range.

1. Use pseudo-linear pharmacokinetics to predict new concentration for a dosage increase:

❑ Because the patient is receiving extended phenytoin sodium capsules, a convenient dosage change would be 100 mg/d and an increase to 500 mg/d is suggested.

❑ **Css new = (D new / D old) Css old**

❑ **Css** $_{new}$ = (500 mg/d / 400 mg/d) 6.2 µg/ml = 7.8 µg/ml.

2. Compute 15–33% factor to account for Michaelis-Menten pharmacokinetics.

❑ Because of Michaelis-Menten pharmacokinetics, the serum concentration would be expected to increase 15%, or 1.15 times, to 33%, or 1.33 times, greater than that predicted by linear pharmacokinetics:

❑ Css = 7.8 µg/ml · 1.15 = 9.0 µg/ml and Css = 7.8 µg/ml · 1.33 = 10.4 µg/ml.

❑ Thus, a dosage increase of 100 mg/d would be expected to yield a total phenytoin steady-state serum concentration between 9–10 µg/ml.

Lab no. six

Problems in clinical PK/PD for immunosuppressant (cyclosporine, tacrolimus)

Example: HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral cyclosporine dose designed to achieve a steady-state cyclosporine trough blood concentration equal to 250 ng/ml.

1- **Estimate clearance:**

✓ Estimate clearance according to disease states and conditions present in the patient.

✓ The mean cyclosporine clearance for adult patients is 6 mL/ min/kg.

✓ CL = 6 ml/min/kg · 75 kg · (60 min/h / 1000 mL/L) = 27 L/h.

2. Compute dosage regimen:

✓ A 12-hour dosage interval will be used for this patient.

✓ Note: ng/ml = µg/L

✓ A conversion constant of 1000 µg/mg is used to change the dose amount to mg.

✓ The dosage equation for oral Tacrolimus is:

✓ $D = (Css \cdot Cl \cdot \tau) / F$

✓ D = (250 µg/L · 27 L/h · 12 h) / (0.3 · 1000 µg/mg) = 270 mg, rounded to 300 mg every 12 hours.

Example: HO is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant patient 2 days post transplant surgery. The patient's liver function tests are normal. Suggest an initial oral Tacrolimus dose designed to achieve a steady-state Tacrolimus trough blood concentration equal to 15 ng/ml.

1. Estimate the clearance:

✓ Estimate clearance according to disease states and conditions present in the patient.

✓ The mean Tacrolimus clearance for adult patients is 0.06 L/h/ kg.

✓ CL = 0.06 L/h/kg · 75 kg = 4.5 L/h.

2. Compute dosage regimen:

✓ A 12-hour dosage interval will be used for this patient.

✓ Note: ng/ml = µg/L

✓ A conversion constant of 1000 µg/mg is used to change the dose amount to mg.

✓ The dosage equation for oral Tacrolimus is:

✓ $D = (Css \cdot Cl \cdot \tau) / F$

✓ D = (15 µg/L · 4.5 L/h · 12 h) / (0.25 · 1000 µg/mg) = 3.2 mg, rounded to 3 mg every 12 hours.

Lab no. seven

Problems in clinical PK/PD of other drugs (lithium, theophylline)

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 400 mg every 12 hours of oral cyclosporine capsules. He has normal liver function. The current steady-state cyclosporine blood concentration equals 375 ng/ml. Compute a cyclosporine dose that will provide a steadystate concentration of 200 ng/ml.

Compute new dose to achieve desired serum concentration:

- Using linear pharmacokinetics
- Total daily dose = 400 mg/dose · 2 doses/d = 800 mg/d):

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

- D_{new} = (200 ng/ml / 375 ng/ml) 800 mg/d = 427 mg/d, rounded to 400 mg/d.
- The new suggested dose would be 200 mg every 12 hrs of cyclosporine capsules to be started at the next scheduled dosing time.

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male renal transplant recipient who is receiving 5 mg every 12 hours of oral Tacrolimus capsules. He has normal liver function. The current steady-state Tacrolimus blood concentration equals 24 ng/ml. Compute a Tacrolimus dose that will provide a steady-state concentration of 15 ng/ml.

Compute new dose to achieve desired serum concentration:

- Using linear pharmacokinetics
- Total daily dose = 5 mg/dose · 2 doses/d = 10 mg/d):

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

- D_{new} = (15 ng/ml / 24 ng/ml) 10 mg/d = 6.3 mg/d, rounded to 6 mg/d.
- The new suggested dose would be 3 mg every 12 hrs of Tacrolimus capsules to be started at the next scheduled dosing time.

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with oral theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 8 µg/ml.

1. Estimate $t_{1/2}$ and $K_{e:}$

❑ These parameters estimated according to disease states and conditions present in the patient.

❑ Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline $t_{1/2}$ is 5 hrs.

❑ The elimination rate constant is computed using the following formula:

❑ $K_e = 0.693/ t_{1/2} = 0.693/5 \text{ h} = 0.139 \text{ h-1}$.

2. Estimate V and CL.

❑ The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight:

❑ $V = 0.5 \text{ L/kg} \cdot 75 \text{ kg} = 38 \text{ L}$.

❑ Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant:

❑ $CL = K_e V = 0.139 \text{ h-1} \cdot 38 \text{ L} = 5.28 \text{ L/h}$.

3. Compute dosage regimen.

❑ Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1).

❑ Because the patient has a rapid theophylline CL and short $t_{1/2}$, the initial dosage interval (τ) will be set to 8 hours.

❑ Note: µg/mL = mg/L

❑ The dosage equation for oral theophylline is:

❑ $D = (Css \cdot CL \cdot \tau)/(F \cdot S)$

❑ $D = (8 \text{ mg/L} \cdot 5.28 \text{ L/h} \cdot 8\text{h}) / (1 \cdot 1) = 338 \text{ mg}$, rounded to 300 every 8 hours.

Example: OI is a 60-year-old, 85-kg (6 ft 1 in) male with emphysema who requires therapy with oral theophylline. He has liver cirrhosis (Child-Pugh score = 11) and normal cardiac function. Suggest an initial theophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10µg/ ml.

1. Estimate $t_{1/2}$ and $K_{e:}$

- These parameters estimated according to disease states and conditions present in the patient.
- Patients with severe liver disease have highly variable theophylline pharmacokinetics and dosage requirements. Hepatic disease destroys liver parenchyma where hepatic drug– metabolizing enzymes are contained, and the expected theophylline $t_{1/2}$ is 24 hours.
- The elimination rate constant is computed using the following formula:
- $K_e = 0.693/ t_{1/2} = 0.693/24 \text{ h} = 0.029 \text{ h-1}$.

2. Estimate V and CL.

- The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight:
  - $V = 0.5 \text{ L/kg} \cdot 85 \text{ kg} = 43 \text{ L}$.
- Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant:
  - $CL = K_e V = 0.029 \text{ h-1} \cdot 43 \text{ L} = 1.25 \text{ L/h}$.

3. Compute dosage regimen.

- Oral sustained-release theophylline tablets will be prescribed to this patient (F = 1, S = 1).
  - The initial dosage interval (τ) will be set to 12 hrs .
  - Note: µg/mL = mg/L
  - The dosage equation for oral theophylline is:
  - $D = (Css \cdot CL \cdot \tau)/(F \cdot S)$
- $D = (10 \text{ mg/L} \cdot 1.25 \text{ L/h} \cdot 12\text{h}) / (1 \cdot 1) = 338 \text{ mg}$, rounded to 150 every 8 hours.

Example: LK is a 50-year-old, 75-kg (5 ft 10 in) male with chronic bronchitis who requires therapy with intravenous theophylline. He currently smokes 2 packs of cigarettes daily, and has normal liver and cardiac function. Suggest an initial intravenous aminophylline dosage regimen designed to achieve a steady-state theophylline concentration equal to 10 µg/ml.

1. Estimate $t_{1/2}$ and K_e:

- ❑ These parameters estimated according to disease states and conditions present in the patient.
- ❑ Cigarette smoke induces the enzyme systems responsible for theophylline metabolism, and the expected theophylline $t_{1/2}$ is 5 hrs.
- ❑ The elimination rate constant is computed using the following formula:
  - ❑ $K_e = 0.693/ t_{1/2} = 0.693/5 \text{ h} = 0.139 \text{ h-1}$.

2. Estimate V and CL.

- ❑ The patient is not obese, so the estimated theophylline volume of distribution will be based on actual body weight:
  - ❑ $V = 0.5 \text{ L/kg} \cdot 75 \text{ kg} = 38 \text{ L}$.
- ❑ Estimated theophylline clearance is computed by taking the product of the volume of distribution and the elimination rate constant:
  - ❑ $CL = K_e V = 0.139 \text{ h-1} \cdot 38 \text{ L} = 5.28 \text{ L/h}$.

3. Compute dosage regimen.

- ❑ Theophylline will be administered as the aminophylline dihydrate salt form (S = 0.8).
  - ❑ Note: µg/mL = mg/L
- ❑ Therapy will be started by administering IV loading dose of aminophylline to the patient:
  - ❑ $LD = (Css \cdot V) / S$
- ❑ $LD = (10 \text{ mg/L} \cdot 38 \text{ L}) / 0.8 = 475 \text{ mg}$, rounded to 500 mg IV over 20–30 minutes.
- ❑ An aminophylline continuous IV infusion will be started immediately after the loading dose has been administered.
  - ❑ Note: µg/ml = mg/L
  - ❑ The dosage equation for intravenous aminophylline is:
  - ❑ $K_0 = (Css \cdot CL)/S$
  - ❑ $K_0 = (10 \text{ mg/L} \cdot 5.28 \text{ L/h}) / 0.8 = 66 \text{ mg/h}$, rounded to 65 mg/h.

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Compute an oral lithium dose for this patient for maintenance therapy.

Estimate the creatinine clearance:

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

$$\text{CrCLest for males} = \frac{(140 - \text{age})\text{BW}}{72 \cdot S_{Cr}}$$

$$= \frac{[(140 - 50y)70kg]}{72.\ 0.9\ mg/dL}$$

= 97 mg/dL

2. Estimate CL:

❑ CL = 0.288 (CrCL)

❑ CL = 0.288 (97 mL/min) = 27.9 L/d

3. Select Steady-state concentration:

❑ For a patient requiring maintenance therapy for bipolar disease the desired lithium concentration would be 0.6–0.8 mmol/L.

❑ A serum concentration equal to 0.6 mmol/L will be chosen for this patient

3. Compute dosage regimen.

❑ Oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/ 300 mg of lithium carbonate) will be prescribed to this patient.

❑ The dosage equation for oral Lithium maintenance dose is:

❑ $D/\tau = (Css \cdot CL)/F$

❑ $D/\tau = (0.6 mmol/L \cdot 27.9 L/d)/1 = 16.7$ mmol/d.

❑ D/τ = (300-mg lithium carbonate/8.12 mmol Li+) 16.7 mmol/d = 617 mg/d, rounded to 600 mg/d of lithium carbonate.

❑ This dose would be given as 300 mg of lithium carbonate every 12 hours.

Example: MJ is a 50-year-old, 70-kg (5 ft 10 in) male with bipolar disease. He is not currently experiencing an episode of acute mania. His serum creatinine is 0.9 mg/dL. Compute an oral lithium dose to treat acute mania for this patient.

1. Estimate the creatinine clearance:

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

$$\text{CrCLest for males} = \frac{(140 - \text{age})\text{BW}}{72 \cdot S_{Cr}}$$

$$= \frac{[(140 - 50y)70kg]}{72.\ 0.9\ mg/dL}$$

= 97 mg/dL

2. Estimate CL:

❑ CL = 0.432 (CrCL)

❑ CL = 0.432 (97 mL/min) = 41.9 L/d

3. Select Steady-state concentration:

❑ For a patient requiring therapy for the acute manic phase of bipolar disease, the desired lithium concentration would be 0.8 – 1 mmol/L.

❑ A serum concentration equal to 0.8 mmol/L will be chosen for this patient

3. Compute dosage regimen.

❑ Oral lithium carbonate will be used (F = 1, 8.12 mmol Li+/ 300 mg of lithium carbonate) will be prescribed to this patient.

❑ The dosage equation for oral Lithium maintenance dose is:

❑ $D/\tau = (Css \cdot CL)/F$

❑ $D/\tau = (0.8\ mmol/L \cdot 41.9\ L/d)/1 = 33.5\ mmol/d.$

❑ D/τ = (300-mg lithium carbonate/8.12 mmol Li+) 33.5 mmol/d = 1238 mg/d, rounded to 1200 mg/d of lithium carbonate.

❑ This dose would be given as 600 mg of lithium carbonate every 12 hours.

Example: YC is a 37-year-old, 55-kg (5 ft 1 in) female with bipolar disease. She is currently not experiencing an episode of acute mania and requires prophylactic treatment with lithium. Her serum creatinine is 0.6 mg/dL. The patient is receiving 900 mg of lithium carbonate at 0800 H, 1400 H, and 2000 H, and her 12hour post-dose steady-state lithium serum concentration equals 1.1 mmol/L. Compute a new lithium dose to achieve a steadystate concentration of 0.6 mmol/L.

1. Use linear pharmacokinetics to predict new concentration for a dosage increase:

- **D new = (Css new / Css old) D old**
- **D_{new}** = (0.6 mmol/L / 1.1 mmol/L) 2700 mg/d = 1473 mg/d, round to 1500 mg/d.
- The patient would be administered 600 mg of lithium carbonate at 0800 H and 2000 H, and 300 mg of lithium carbonate at 1400 H.

REFERENCES

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