PHARMACOKINETICS SMALL GROUP II:

Question 1
Why are some drug therapies initiated with a loading dose?

Answer:
Emphasize that LD establishes initial therapeutic level quickly.

The time to reach the steady-state target concentration is approximately 4-6 elimination half-lives. In some cases, a loading dose may be given to more rapidly achieve a therapeutic plasma concentration. This is only required for drugs that are administered at intervals of less than 4 elimination half-lives.

The loading dose is dependent on volume of distribution rather than clearance and is intended to rapidly achieve a specific concentration of drug to elicit a therapeutic effect:

\[ LD = \frac{V_d \times TC}{S \times F} \]

where LD = loading dose (e.g. in mg), \( V_d \) = volume of distribution (e.g. in L), TC = target concentration (e.g. in mg/L), F = bioavailability, S = Salt Factor.

Question 2
What’s the difference between loading dose and maintenance dose?

Answer:
Emphasize that MD provides sustained plasma concentrations within the therapeutic range.

Maintenance dosing is a regimen whereby a drug is administered at regular intervals (or continuously infused) to achieve a target steady-state plasma concentration. When drugs are administered at an interval that greatly exceeds their elimination half-life, large fluctuations in the plasma concentration, above and below the steady-state target concentration, will be achieved.

Once steady-state is achieved, the maintenance dose matches the amount of drug cleared since the previous dose was administered (or the infusion rate matches the rate of elimination). Maintenance dosing is therefore dependent on the clearance of elimination according to the formula:

\[ MD = \frac{CL \times TC \times T}{S \times F} \]

where MD = maintenance dose (e.g. in mg), CL = clearance of elimination (units of flow, e.g. L/hr), TC = target concentration (at steady-state; units of concentration, e.g. mg/L), T = interval (units of time, e.g. hr), and F = bioavailability, S = Salt Factor.
QUESTION 3
What oral loading dose of digoxin tablets (70% bioavailability) will be required to achieve a plasma concentration of 1.5 µg/L in a 70 kg male patient if the volume of distribution of digoxin in this patient is 7.3 L/kg.

Answer:

$$LD = \frac{V_d \times TC}{S \times F} = \frac{7.3 \text{ L/kg} \times 70 \text{ kg} \times 1.5 \mu g/L}{1 \times 0.7} = 1095 \mu g$$

QUESTION 4
100 mg of a drug with a bioavailability of 50% is given every 12 hrs to a patient. The volume of distribution of the drug is 100 L and the half-life is 12 hrs. Based upon this information calculate the steady state concentration of the drug in the patient?

Answer:

$$C_{ss} = \frac{S \times F \times \text{Dosing rate}}{CL}$$

Since $CL = V_d \times k$

$$C_{ss} = \frac{S \times F \times \text{Dosing rate}}{V_d \times k}$$

$$k = \frac{0.693}{t_{1/2}} = \frac{0.693}{12} = 0.05775 \text{ hr}^{-1}$$

$$\therefore C_{ss} = \frac{1 \times 0.5 \times 100 \text{ mg/12hr}}{100 \text{ L} \times 0.05775 \text{ hr}^{-1}} = 0.72 \text{ mg/L}$$
QUESTION 5
P.T. is a 2-week old, 3.2 kg neonate who has developed idiopathic tonic clonic seizure activity. It is decided that P.T. will be treated with phenobarbital, a long-acting barbiturate that can be used to treat seizures. An i.v. loading dose of 20 mg/kg phenobarbital sodium is given followed by maintenance doses of 1.5 mg/kg every 12 hrs.

Using the following pharmacokinetic data:
- Volume of distribution of phenobarbital is 0.9 L/kg for neonates
- Phenobarbital clearance is 0.004 L/kg/hr for neonates
- Salt factor for phenobarbital sodium is 0.9

5A. Calculate the initial post-load phenobarbital plasma concentration that results from the initial loading dose.

Answer:
\[
\text{LD} = \frac{V_d \times TC}{S \times F}
\]

\[
TC = \frac{LD \times S \times F}{V_d} = \frac{20 \text{ mg/kg} \times 3.2 \text{ kg} \times 0.9}{0.9 \text{ L/kg} \times 3.2 \text{ kg}} = 20 \text{ mg/L}
\]

5B. Calculate the average steady state concentration of phenobarbital that results from the maintenance doses.

Answer:
\[
C_{ss} = \frac{S \times F \times \text{Dose/interval}}{CL}
\]

First need to determine CL in P.T.

\[
CL = 0.004 \text{ L/kg/hr} \times 3.2 \text{ kg} = 0.013 \text{ L/hr}
\]

\[
C_{ss} = \frac{0.9 \times (1.5 \text{ mg/kg} \times 3.2 \text{ kg})/12\text{hrs}}{0.013 \text{ L/hr}} = 27.69 \text{ mg/L}
\]
Question 6.
RJ is a 29-year old, 63 kg female, 5 ft. 4 inches in height, who presents to the Emergency Room for the treatment of severe respiratory distress. The patient has a history of asthma, and has been taking her albuterol metered dose inhaler every hour for the past 6 hours without relief. Her other medications include theophylline (TheoDur®) 300mg PO Q12hr and norgestrel (Ovrette®) one tablet daily for contraception. The patient admits to smoking one pack of cigarettes daily for the past 2 years, and is relatively noncompliant with her theophylline (TheoDur®) therapy. Upon arrival in the Emergency Room, the patient is given albuterol respiratory treatments, a 125mg intravenous dose of methylprednisolone, and a theophylline level is ordered.

Use the pharmacokinetic parameters for theophylline listed below to answer the following questions:

- \( V_d = 0.5 \text{ L/kg} \) (use lean body weight)
- \( CL = 0.064 \text{ L/hr/kg} \) for smoking adults
- \( t_{1/2} = 5.3 \text{ hours} \) for smoking adults

6A. The serum theophylline level was reported from the lab as 3.5 mg/L. Calculate an intravenous loading dose of theophylline to achieve a serum theophylline concentration of 15 mg/L.

Answer:
Emphasize that Theophylline has a narrow therapeutic index. Concentration on board (3.5mg/ml) must be taken into consideration to avoid potential toxicity.

\[
\text{LBW} = 45.5 + (2.3 \times 4) = 54.7\text{kg}
\]

\[
\text{Adjusted LD} = \frac{V_d \times [C_{\text{desired}} - C_{\text{initial}}]}{S \times F} = \frac{(0.5 \text{ L/kg}) \times (54.7\text{kg}) \times (15 \text{ mg/L} - 3.5 \text{ mg/L})}{1} = 315 \text{ mg or round to 300 mg loading dose of theophylline}
\]

Albuterol: \( \beta_2 \) adrenergic agonist (bronchodilator)
Theophylline: adenosine receptor antagonist & phosphodiesterase inhibitor (bronchodilator)
Norgestrel: progestin (contraceptive)
Methylprednisolone: corticosteroid (anti-inflammatory)
6B. Determine a theophylline maintenance infusion rate (mg/hr) to achieve a steady-state theophylline concentration of 12 mg/L.

Answer:
Emphasize that i.v. infusion will produce a gradual increase in plasma levels that will stabilize at steady-state levels after approximately 4 elimination half-lives.

\[
\text{Dosing rate} = \frac{\text{CL} \times C_{ss}}{S \times F}
\]

\[
= \frac{(0.064 \text{ L/hr/kg}) (54.7 \text{ kg}) (12 \text{ mg/L})}{1}
\]

\[
= 42 \text{ mg/hour infusion of theophylline}
\]

6C. Despite your recommendations, the patient is started on a theophylline infusion of 60 mg/hour. Her steady-state serum theophylline concentration (17 mg/L) on this dose was within the normal therapeutic range (10-20 mg/L), however, the patient has been complaining of nausea, insomnia, and nervousness. Calculate a new maintenance infusion of theophylline to reduce the serum concentration to 12 mg/L.

Answer:
Emphasize that steady-state plasma concentrations can be adjusted by a proportional adjustment of the maintenance dose.

Theophylline has a narrow therapeutic index and it is not uncommon for patients to exhibit symptoms of toxicity despite ‘therapeutic’ levels. Theophylline pharmacokinetics are first-order within the therapeutic range. During stable conditions when CL remains fixed, there is a proportionality between maintenance dose and C_{ss}. Therefore, once steady-state is achieved, any dosage changes should produce a proportional change in theophylline serum concentration.

\[
\frac{\text{Dose}_1}{C_1} = \frac{\text{Dose}_2}{C_2}
\]

\[
\frac{60 \text{ mg/hr}}{17 \text{ mg/L}} = \frac{X}{12 \text{ mg/L}}
\]

\[
X = 42 \text{ mg/hr.}
\]

Current theophylline infusion should be stopped until symptoms resolve then resumed at 42 mg/hr.
**Question 7.**

MR is a 36-year old non-obese female (60kg) who presents to the hospital with a 3-day history of high fevers (103°F) and shaking chills. MR recently underwent a dental procedure and has valvular heart disease. On exam, a new cardiac murmur is identified. Four sets of blood cultures were drawn and all were found to be growing *Pseudomonas aeruginosa*. It is thought that the patient most likely has pseudomonal endocarditis, and antibiotic therapy with tobramycin will be initiated. Tobramycin therapy is usually administered at 8 hr intervals.

Use the population pharmacokinetic parameters below to answer the following questions.

\[ V_d \text{ of tobramycin} = 0.25 \text{ L/kg} \]
\[ t_\frac{1}{2} \text{ of tobramycin} = 2 \text{ hours} \]

7A. Calculate a loading dose of tobramycin to achieve a peak serum concentration of 8.0 mg/L for the treatment of gram negative infections in MR assuming “normal” tobramycin pharmacokinetic parameters.

**Answer:**

*Emphasize that Loading Dose is dependent on Volume of Distribution.*

**Note:** LBW (lean body weight) should be utilized for aminoglycoside dosing as they do not distribute into adipose tissue. Since MR is non-obese actual body weight can be used to calculate LD

\[
LD = \frac{V_d \times TC}{S \times F} \quad F=1 \text{ for intravenous administration}
\]

\[
= \frac{(0.25 \text{ L/kg}) (60\text{kg}) (8.0\text{mg/L})}{1} = 120 \text{ mg}
\]

7B. Tobramycin therapy is normally initiated as a maintenance dose administered every 8 hours. In adults with normal renal function this yields a trough level of less than 2 mg/L. Calculate MR’s expected serum concentration (trough level) of tobramycin 8 hours after the 8.0 mg/L peak concentration achieved with the loading dose. What peak and trough values would be expected following administration of the same dose 8 hr after the first dose?

**Answer:**

*Emphasize that the exponential 1st order rate equation can be used to predict future concentrations based on measured concentrations at a point in time.*

**Aminoglycosides exhibit first-order kinetics of elimination:**

\[
C = C_0 e^{-kt}
\]
\[
k = \frac{0.69}{t_\frac{1}{2}} = \frac{0.69}{2\text{hr}} = 0.35\text{hr}^{-1}
\]
Co = 8.0 mg/L
-kt = (-0.35hr⁻¹ x 8hr) = -2.8
C = 8.0mg/L e⁻².⁸
  = 8.0mg/L x 0.06 = 0.5mg/L

A simpler approach is simply to recognize that 8 hr equals 4 elimination half lives, so the concentration should decrease 16-fold (2⁴), from 8 to 0.5 mg/L.

Rearrange the “Adjusted Loading Dose” formula to determine the peak concentration for the second dose:

LD = \( \frac{V_d \times (C_{\text{Peak}} - C_{\text{trough}})}{S \times F} \)

120 mg = 0.25L/kg x 60kg (\(C_{\text{Peak}} - 0.5\)mg/L)

120 mg/15L = \(C_{\text{Peak}} - 0.5\)mg/L

\(C_{\text{Peak}} = 8.5\)mg/L

The trough concentration following this peak can then be determined as above:

C = \(C_0 \times e^{-kt}\)

k = 0.69/tᵢ₅ = 0.69/2hr = 0.35hr⁻¹

\(C_0 = 8.5\)mg/L

-kt = (-0.35hr⁻¹ x 8hr) = -2.8

C = 8.5mg/L e⁻².⁸
  = 8.5mg/L x 0.06 = 0.5mg/L

7C. MR’s tobramycin levels are measured 8hr after the initial peak of 8.0mg/L and found to be 4.0 mg/L. What could account for this difference from the expected value calculated in the previous question? Assuming a normal volume of distribution, calculate an adjusted loading dose of tobramycin to provide a peak concentration of 8.5mg/L from the 4.0 mg/L measured level.

Answer:
Emphasize that dosing regimens are often based on population averages of Vₐ and CL, but individual patients may not fit the “average” and hence dosing may require adjustments.

The elevated trough value may result from decreased clearance (most likely) and/or increased volume of distribution. Aminoglycosides are eliminated almost exclusively by the kidney, so decreased clearance may be an indication of renal failure.
Use the “Adjusted Loading Dose” formula:

\[ LD = V_d \times \frac{[C_{\text{desired}} - C_{\text{initial}}]}{F \times S} \]

\[ = 0.25L/kg \times 60kg \times [8.5mg/L - 4.0mg/L] = 67.5mg \]

7D. Maintenance dosing is generally intended to achieve a steady state (amount of drug administered equals the amount of drug eliminated since the previous dose). Calculate an 8hr maintenance dosing regimen for MR and for a patient with “normal” tobramycin pharmacokinetic parameters to achieve a steady-state target concentration of 2.9 mg/L.

Answer:
Emphasize that Maintenance Dose is dependent on Clearance. Must determine MR’s Clearance to adjust Maintenance Dose.

Maintenance Dose = \( \frac{CL \times TC \times T}{S \times F} \)

\[ CL = \frac{V_d \times k}{S \times F} \]

For MR:
First determine time constant for elimination for MR:
\[ C = C_0 \times e^{-kt} \]
\[ \frac{C}{C_0} = e^{-kt} \]
\[ \ln\left[\frac{C}{C_0}\right] = -kt \]
\[ k = -\ln\left[\frac{C}{C_0}\right]/t = -\ln\left[\frac{4.0}{8.0}\right]/8hr = 0.087hr^{-1} \]
Then determine CL and calculate MD:
\[ CL = V_d \times k = 0.25L/kg \times 60kg \times 0.087hr^{-1} = 1.3L/hr \]
\[ MD = 1.3L/hr \times 2.9mg/L \times 8hr = 30mg \]

For “normal patient”:
\[ CL = V_d \times k = 0.25L/kg \times 60kg \times 0.35hr^{-1} = 5.2L/hr \]
\[ MD = 5.2L/hr \times 2.9mg/L \times 8hr = 120mg \]

7E. How soon should a maintenance dose be started after the loading dose is administered?

Answer:
Maintenance dosing is initiated at its normal dosing interval after the loading dose. In this case the dosing interval is 8 hr, so the first maintenance dose should be administered 8 hr after the loading dose. Administering the maintenance dose immediately following the loading dose will result in supratherapeutic levels and potential toxicity.
7F. If MR were given the “normal patient” maintenance dosing regimen calculated in 6D, what steady-state target concentration of tobramycin would be expected?

**Answer:**

**Emphasize that maintaining a “normal” dosing regimen in a patient with reduced Clearance can result in toxic concentrations of the drug in that patient.**

\[ \text{Maintenance Dose} = CL \times TC \times T/F \]

\[ CL = V_d \times k = 0.25 \text{L/kg} \times 60 \text{kg} \times 0.087 \text{hr}^{-1} = 1.3 \text{L/hr} \]

\[ TC = \frac{MD \times F}{CL \times T} = \frac{120 \text{mg} \times 1}{1.3 \text{L/hr} \times 8 \text{hr}} = 11.5 \text{mg/L} \]

7G. Laboratory tests reveal that M.R. is suffering from renal impairment. Since aminoglycosides such as tobramycin are eliminated almost exclusively via the kidney, impaired renal function will act to significantly reduce the clearance of these drugs in such patients. Hence, administration of a normal dosing rate of 2mg/kg every 8 hours to a patient with impaired renal function can potentially result in the accumulation of toxic levels of drug.

What are the two main methods in which the dosing regimen of a drug can be altered in patients with impaired clearance, and how will these changes affect serum concentrations compared to the original dosing regimen?

**Answer:**

**Emphasize that maintenance dosing is dependent on Clearance—if CL changes, MD or interval must be adjusted to stay within the therapeutic range.**

- **DECREASING DOSE (SAME INTERVAL): REDUCES PEAK; TROUGH VALUES HIGHER THAN THOSE OBTAINED WITH ORIGINAL CLEARANCE**
- **SAME DOSE, INCREASE DOSING INTERVAL: BOTH PEAK AND TROUGH VALUES ARE RESTORED TO VALUES EXPECTED WITH ORIGINAL CLEARANCE**
- **INTERMEDIATE DOSE, INTERMEDIATE DOSING INTERVAL: LOWER PEAK AND SLIGHTLY HIGHER TROUGH VALUES**

These effects can be predicted based on the Maintenance Dosing Equation:

\[ \text{Maintenance Dose} = CL \times TC \times T \]

\[ TC = \frac{MD}{CL \times T} \]

if CL is decreased, TC can be maintained by decreasing MD or by increasing T.
7H. Since aminoglycosides are eliminated by the kidneys, creatinine clearance can be used to estimate the extent of renal impairment (relative reduction of tobramycin clearance) and to adjust the dosing rate accordingly. In the case of M.R. her serum creatinine concentration is reported to be 2.98 mg/dL. Based upon this information calculate the revised dosing rate for tobramycin in this patient.

Answer:
Emphasize that creatinine clearance can be used to estimate the patient’s ability to clear drugs that are eliminated by the kidney.

To calculate the tobramycin dosing rate for MR, first assess the pt’s renal function by calculating the creatinine clearance (CrCl) in ml/min:

\[
\text{Cockcroft & Gault Eq:} \\
\text{CrCL (ml/min) = } \frac{(140- \text{age}) \times \text{wt (kg)}}{72 \times [\text{serum Cr}] \text{ (mg/dL)}} \times 0.85
\]
= 29.1ml/min × 0.85 (female) = 24.7ml/min

MR’s creatine clearance is less than normal (normal CrCL is 100 ml/min), suggesting a degree of renal failure (RF). Therefore the dosing rate should be adjusted according to the following formula:

\[
\text{Dosing Rate}_{RF} = \text{Dosing Rate}_{Normal} × \frac{\text{CrCL}_{RF}}{\text{CrCL}_{Normal}}
\]

Dosing Rate_{MR} = 2mg/kg every 8hr × \frac{25}{100} = 0.5mg/kg every 8hr

Alternatively, the dosing rate interval can be adjusted in proportion to the reduction in CrCL:

\[
T_{RF} = T_{Normal} × \frac{\text{CrCL}_{Normal}}{\text{CrCL}_{RF}} = 8hr × \frac{100}{25} = 32hr
\]

Note that the interval calculated is LONGER than the interval for patients without renal impairment. A 32hr interval is impractical; ask students to design a more practical dosing regimen, e.g. make the interval 24 hr and adjust the MD accordingly:

0.5mg/kg every 8hr is equivalent to 1.5mg/kg every 24hr

This dosing regimen represents a combination of decreased dose (From 2.0mg/kg to 1.5mg/kg) and an increase in interval (from 8hr to 24hr) to