DETERMINATION OF DOSE AND DOSING INTERVAL

K.P. ARUN
LECTURER

DEPARTMENT OF PHARMACY PRACTICE
JSS COLLEGE OF PHARMACY
OOTY

INTRODUCTION

- The dose of a drug is the amount at the time of administration to obtain a desired therapeutic response
- Dosage regimen refers to the schedule of dosing
- Generally, the manufacturers provides a range of doses for a given drug
- Since, several factors affecting the dose of a drug, the exact amount of a drug to be administered is decided by the health care professionals
- The dose of a given drug is specific to the patient
- Thus, a fixed dose of a drug might be an overdose in some patients, whereas the same dose might be considered an under-dose in another group of patients
- The inter and intra subject variations to the effects of drugs can be avoided by tailoring a dose (or a dosage regimen) to a given patient through the use of clinical pharmacokinetics

INTRODUCTION…

- Some of the factors affecting the dose of a drug include

Pharmaceutical factors

- ✓ Type of dosage form
- ✓ Route of administration

Patient related factors

- ✓ Individual patient's tolerance of the drug
- ✓ Genetic predisposition
- ✓ Concurrent administration of other drugs
- ✓ Patient's age, body weight, gender
- ✓ Length of illness
- ✓ General physical health
- ✓ Liver and kidney function in the patient

Pharmacokinetic factors

- ✓ Rate and extent of
  - Absorption
  - Distribution
  - Metabolism and
  - Excretion of drugs in patients

INTRODUCTION…

- For an optimal therapeutic response, we must select a suitable drug and determine an appropriate dose with the available strengths and a convenient dosing interval

- To meet this responsibility, the serum or plasma drug concentrations have to be analyzed, pharmacokinetic parameters have to be evaluated, the drug dose has to be adjusted and the dosing interval has to be determined

Pharmacokinetic-Based Design and Modification of Dosage Regimens:

- Traditionally, drug information provided by pharmaceutical companies (such as package inserts and Physicians' Desk Reference) has contained information about the pharmacokinetics of drugs and the therapeutic range (if available)
- Depending on this information, the focus of design of dosage regimens has been the use of pharmacokinetic data

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

IV Bolus Dosing:

STEP – 1: Estimation of a target average steady state concentration(C_{ave}^{∞}):

- The following equation defines C_{ave}^{∞} the value based on the minimum (C_{min}^{∞}) and maximum (C_{max}^{∞}) steady state concentrations equal to MEC and MTC, respectively

$$C_{ave}^{\infty} = C_{max}^{\infty} - C_{min}^{\infty} / \ln (C_{max}^{\infty} / C_{min}^{\infty})$$

- We should note that the C_{ave}^{∞} is slightly different from an algebraic average of C_{min}^{∞} and C_{max}^{∞}

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

- This is because the plasma concentrations of drugs with first order elimination decline exponentially instead of a simple linear decline

STEP – 2: Estimation of the dosing rate (dose/τ) necessary to achieve C_{ave}^{∞}:

- For this calculation, one also needs clearance (Cl) and extent of systemic availability (F) of the drug

$$\text{Dose} / \tau = Cl \cdot C_{ave}^{\infty} / F$$

For IV administration, F is equal to 1. Therefore,

$$\text{Dose} / \tau = Cl \cdot C_{ave}^{\infty}$$

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

STEP – 3: Estimation of the maximum allowable τ (τ_{max})

- The rate of decline in the plasma concentration from C_{max}^{∞} to C_{min}^{∞} is governed by the drug elimination half life ($t_{1/2}$) or elimination rate constant (K)

- Therefore, we can estimate how long it would take for the plasma concentration to decline from a maximum to a minimum

$$C_{min}^{\infty} = C_{max}^{\infty} e^{-k\tau_{max}}$$

The above equation can be rearranged to solve for τ_{max}:

$$\tau_{max} = \ln (C_{max}^{\infty} / C_{min}^{\infty}) / K$$

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

- Choose a practical value based on the calculated τ_{max}
- The τ_{max} calculated is the longest interval that may be selected for the patient
- But, the drug administration at every τ_{max} hour is not practical
- Hence, a τ should be selected from one of the following more practical values: viz., 4, 6, 8, 12, or 24 hours
- Obviously, we will choose a longer τ if possible (for patient and staff convenience)
- However, a selected practical τ cannot be more than τ_{max} if the desired outcome is to keep the plasma concentrations between C_{min}^{∞} and C_{max}^{∞}

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

STEP – 4: Estimation of the dose:

- Knowing the dosing rate (dose/τ) and dosage interval (τ), we can simply estimate the dose as

Dose = Dosing Rate x Dosage Interval

- If the dose is not practical or the available strengths would not allow the administration of the exact dose, we may round it to the nearest practical number

- **Re-estimate C_{ave}^{∞}, C_{min}^{∞}, and C_{max}^{∞} based on the selected τ and dose**

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

- To estimate C_{min}^{∞} and C_{max}^{∞} values with the practical regimen, first, the C_{max} and C_{min} after the first dose (C_{max}^{1st} and C_{min}^{1st} respectively) are estimated

$$C_{max}^{1st} = Dose / V$$

$$C_{min}^{1st} = C_{max}^{1st} . e^{-K\tau}$$

- Then, using the accumulation factor (R), the C_{max}^{∞} and C_{min}^{∞} values are predicted as shown below

$$R = 1 / (1 - e^{-K\tau})$$

$$C_{max}^{\infty} = C_{max}^{1st} . R$$

$$C_{min}^{\infty} = C_{min}^{1st} . R$$

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

STEP – 5: Estimation of the loading dose (if needed):

- In some cases, administration of a loading dose may be necessary, particularly if the half life of the drug is long and the immediate achievement of therapeutic concentrations is important

- In these cases, the loading dose (D_L)may be estimated by either of the following two methods

$$D_L = D_M \cdot R$$

$$D_L = C_{max}^{\infty} \cdot V$$

Where, D_M = maintenance dose; R = Accumulation factor; V = Volume of distribution

- As mentioned earlier, the dose should be adjusted based on the available strengths and/or salts of the drug

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

Constant IV Infusion:

- This is the simplest case, as one deals with the infusion rate constant (R_0) only (no need to estimate τ)

- The following procedure may be used for this process:

STEP – 1: Estimation of infusion rate constant (R_0):

- R_0 can be calculated based on the desired steady state concentration (C_{ss}) and the drug clearance

$$R_0 = Cl \cdot C_{ss}$$

- The desired C_{ss} is normally a concentration within the MEC and MTC values

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

STEP – 2: Estimation of loading dose(D_L):

- D_L can be calculated based on the C_{ss} and V of the drug

$$D_L = C_{ss} \cdot V$$

- The desired is normally a concentration within the MEC and MTC values

- Administration of D_L should produce a concentration of C_{ss} which is maintained by simultaneous start of the infusion at a rate of R_0

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

Intermittent IV Infusion:

- Few drugs (aminoglycosides and some other antibiotics such as vancomycin) have to be usually administered via multiple shorts (30-60 min) IV infusions at regular intervals

- Generally, for antibiotics, the desired C_{max} is a value several fold above the minimum inhibitory concentration of the drug for the responsible organism

- However, C_{min} is usually significantly lower than the minimum inhibitory concentration

- For these antibiotics, it is desired to design a dosage regimen to have a C_{min}^{∞} value above the MIC of the drug and a C_{max}^{∞} value at or below a concentration associated with toxicity

- The approach for selection of a dosage interval is, therefore, slightly different from that used earlier for the design of dosage regimens to produce concentrations within a therapeutic range (MEC and MTC)

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

Extravascular Administration:

- The estimation of dose and dosing rate after extravascular dosing (e.g., oral administration) is more complicated than that after IV bolus doses because the rate and extent (F) of extravascular availability would also be important factors in addition to other kinetic parameters
- One extreme case for extravascular dosing is when the absorption is so fast that it can be assumed as instantaneous for practical purposes
- This case would be similar to IV bolus administration with F of 1
- Because of the complexity of calculations involving absorption rate constant, in practice, the absorption of most immediate release formulations is assumed to be instantaneous
- Therefore, the equations used for IV bolus dosing can also be used for design of extravascular dosage regimens with reasonable accuracy

Pharmacokinetic-Based Design and Modification of Dosage Regimens…

- In fact, the actual fluctuation in the plasma samples after extravascular dosing would be less than that estimated using instantaneous absorption or IV administration

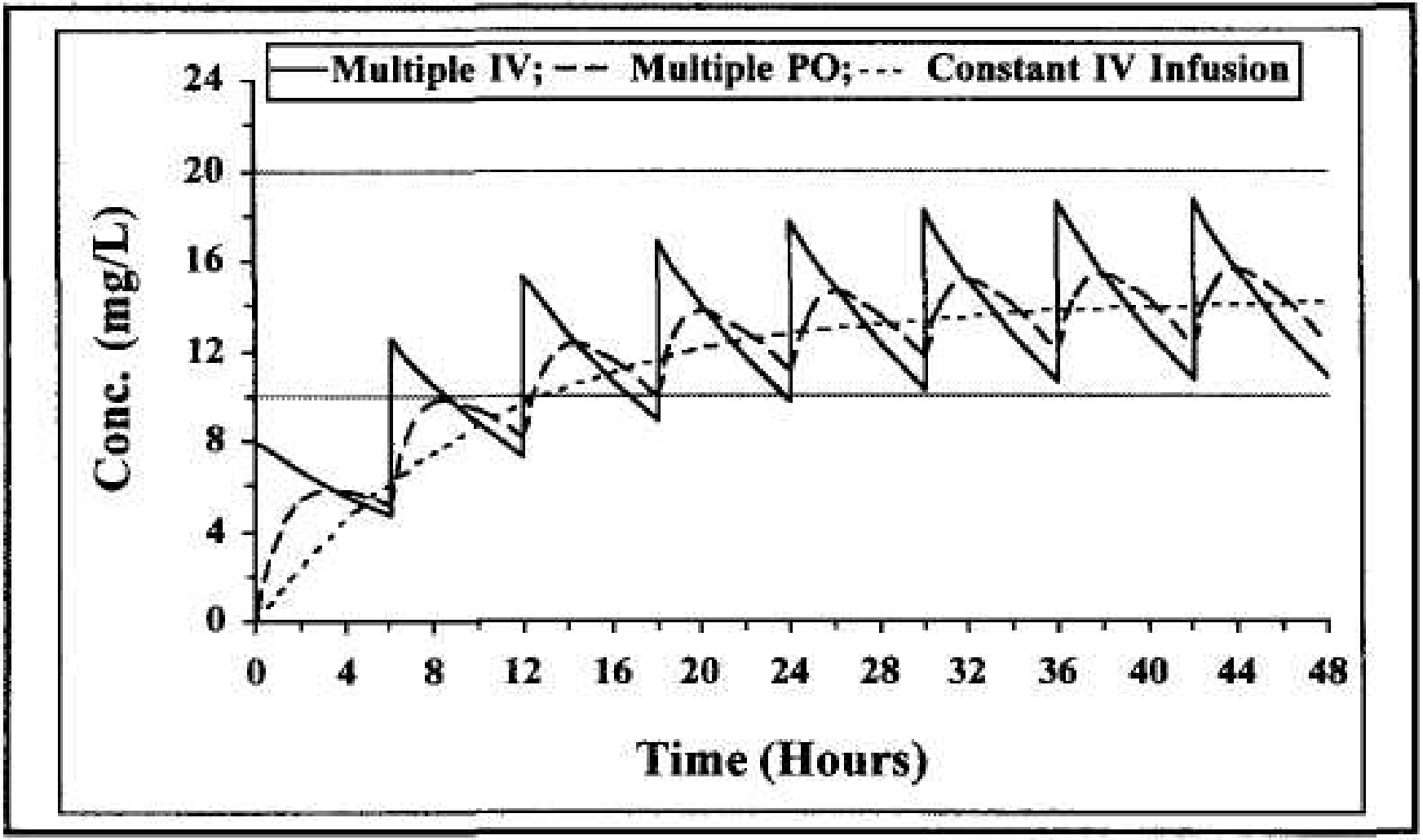
- This is because in reality, absorption takes place over a certain period of time resulting in lower C_{max}^{∞} values than those estimated from an instantaneous absorption

- Also, the gradual absorption of the drug from the site of administration (e.g., gastrointestinal tract) results in higher C_{min}^{∞} values after extravascular dosing, compared with IV administration of the same dose

- Generally, slower absorption profiles would result in less fluctuation

- In another extreme, the profiles after controlled release formulations (e.g., zero-order absorption) would result in almost constant concentrations at steady state with minimal fluctuation, a situation similar to constant IV infusion

- In these cases, the constant infusion equations may be used for the prediction of dosage regimens of controlled release products



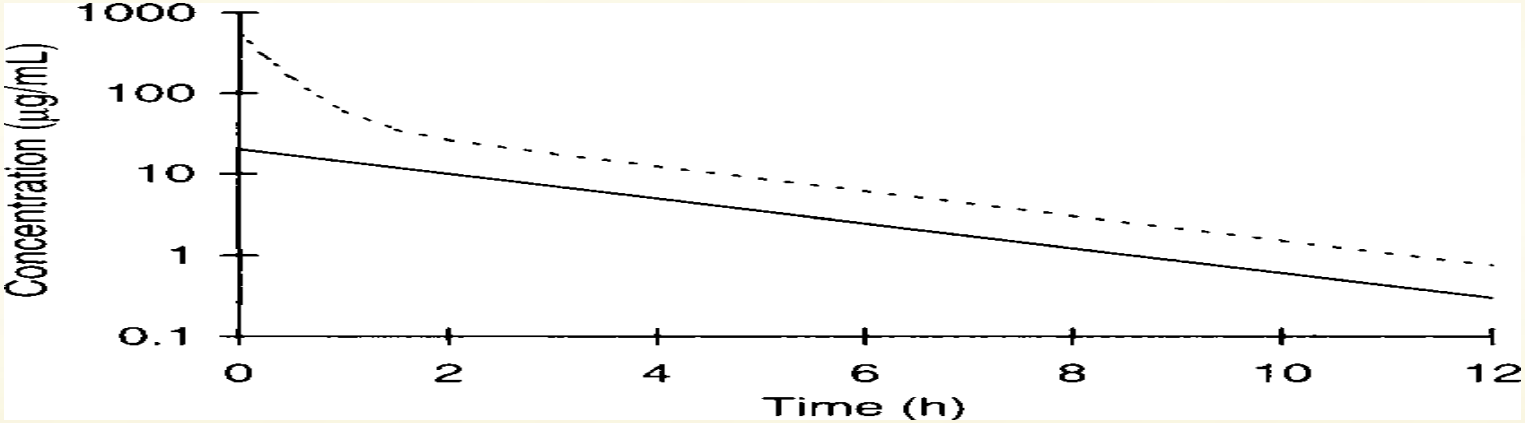
Simulated plasma concentration-time courses of an example drug after the IV bolus and PO administration of 280-mg doses every 6 hr and after constant IV infusion of 46 mg/hr

Equations to Compute Individualized Dosage Regimens for Various Routes of Administration

ROUTE OF ADMINISTRATION	DOSAGE INTERVAL (τ), MAINTENANCE DOSE (D or R_0), AND LOADING DOSE (D_L) EQUATIONS
Intravenous bolus	$\tau = \ln (C_{max}^{\infty} / C_{min}^{\infty})/K$ $D = C_{max}^{\infty} . V. (1-e^{-K\tau})$ $D_L = C_{max}^{\infty} . V$
Continuous intravenous infusion	$R_0 = C_{ss} . Cl = Css . K . V$ $D_L = C_{ss} . V$
Intermittent intravenous infusion	$\tau = [\ln (C_{max}^{\infty} / C_{min}^{\infty})/K] + t'$ $R_0 = Css . K . V [(1-e^{-K\tau})/ (1-e^{-Kt'})]$ $D_L = R_0/(1-e^{-K\tau})$
Extravascular	$\tau = [\ln (C_{max}^{\infty} / C_{min}^{\infty})/K] + T_{max}$ $D = [(C_{max}^{\infty} .V)/F][(1-e^{-K\tau})/e^{-K T max}]$ $D_L = C_{max}^{\infty} . V /F$
Average steady-state concentration (any route of administration)	$D = (C_{ss} . Cl . \tau)/F = (C_{ss} . K . V . \tau)/F$ $D_L = C_{ss} . V / F$

MULTICOMPARTMENT MODEL

- A two compartment model is the simplest of the multicompartment models
- When serum concentrations decrease in a rapid fashion initially and then decline at a slower rate later, a multicompartment model can be used to describe the serum concentration/time curve



- The solid line shows the serum concentration/time graph for a drug that follows one-compartment model pharmacokinetics after intravenous bolus administration
- Drug distribution occurs instantaneously, and serum concentrations decline in a straight line on semi logarithmic axes

MULTICOMPARTMENT MODEL…

- The dashed line represents the serum concentration/time plot for a drug that follows two compartment model pharmacokinetics after an intravenous bolus is given
- Immediately after the dose is given, serum concentrations decline rapidly and this portion of the curve is known as the distribution phase
- During this phase, drug is distributing between blood and tissues and is removed from the body via hepatic metabolism and renal elimination
- After this phase of the curve is finished, drug distribution is nearly complete and a psuedoequilibrium is established between the blood and tissues
- Later, serum concentrations decline more slowly during the elimination phase, in which drug is primarily being removed from the body

MULTICOMPARTMENT MODEL…

- Similar equations for a two compartment model are available for intravenous (bolus & infusions) and extravascular doses as that of one compartment model

- In order to get accurate values for the pharmacokinetic constants in the equation, 3–5 serum concentrations for each phase of the curve need to be obtained after a dose is given to a patient

- Because of the cost and time involved to collect 6–10 serum concentrations after a dose, multicompartment models are rarely used in patient care situations

- If a drug follows multicompartment pharmacokinetics, serum concentrations are usually not drawn for clinical use until the distribution phase is over and the elimination phase has been established

- In these cases, it is possible to use simpler one compartment model equations to compute doses with an acceptable degree of accuracy

Pharmacodynamic-Based Dosage Regimen Design

- Recently, very specific pharmacodynamic information such as maximum effect (E_{max}) and the plasma concentration producing half of E_{max} (EC_{50}) are beginning used in dosage regimen design

- Therefore, it is possible to design dosage regimens for these drugs to achieve certain effects rather than certain concentrations

- For example, the so called E_{max} model equation, relating E_{max}, EC_{50}, and the plasma concentration (C) producing a certain effect (E) may be used to translate the desired upper (E_{UPPER}) and lower (E_{LOWER}) effects (goal of therapy) to C_{max}^{∞} and C_{min}^{∞} values

Pharmacodynamic-Based Dosage Regimen Design

$$E = E_{max} \cdot C / EC_{50} + C$$

$$C = EC_{50} \cdot E / E_{max} - E$$

$$C_{max}^{\infty} = EC_{50} \cdot E_{UPPER} / E_{max} - E_{UPPER}$$

$$C_{min}^{\infty} = EC_{50} \cdot E_{LOWER} / E_{max} - E_{LOWER}$$

- The estimated C_{max}^{∞} and C_{min}^{∞} values then can be used for the design of multiple dosing regimens as explained earlier

- Similarly, for the constant IV infusion, a target effect may be converted to a C_{ss} value and a constant infusion rate be estimated as explained earlier

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT

Changing Dose:

- The following simple equation does not require a calculator, and can be done in most cases within few seconds, assuming serum concentrations were measured appropriately

$$\text{New Dose} = \frac{\text{Desired Concentration}}{\text{Measured Concentration}} \times \text{Old Dose}$$

- This equation is based on the fact that increase or decrease in doses (keeping the interval the same) produce proportional changes in peaks, troughs, or steady state serum concentrations

- In other words, if the dose is doubled, peak and trough concentrations are also doubled

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT…

- This proportional dose approach is pharmacokinetically correct if the following conditions are met
  - Serum concentrations are measured at steady state and are correctly and accurately drawn
  - The drug follows first-order and one-compartmental pharmacokinetics
  - The dosing interval is not changed
  - Infusion times of the present dosage and the times of concentrations measured are the same for the new dosage within reason, say, plus or minus 5-10 minutes
- With this method one does not have to worry about exponential functions, infusion rates, half-lives, volume of distribution, elimination rate constants

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT…

Table 1. Dosage Adjustment Examples for Patients Receiving Intravenous Drugs by Bolus or Infusion

	Present Dosing Regimen as Bolus or Infusion over Y Minutes	Peak Concentration Measured X Minutes after End of Bolus or Infusion	Trough Concentration Measured Z Minutes before next Bolus or Infusion	New Dosing Regimen	Peak Concentration that Will Be Achieved with New Dosage X Minutes after End of Bolus or Infusion	Trough Concentration that Will Be Achieved Z Minutes before next Bolus or Infusion
Ex 1	80 mg q8h	6.5 mg/L	1.2 mg/L	120 mg q8h	120/80 x 6.5 = 9.8 mg/L	120/80 x 1.2 = 1.8 mg/L
Ex 2	1000 mg q12h	42 mg/L	16 mg/L	750 mg q12h	750/1000 x 42 = 32 mg/L	750/1000 x 16 = 12 mg/L

Changing Dose and Dosing Interval:

- This can be done almost as simply as the above examples by applying couple of pharmacokinetic principles

Step 1: Determine the New Dose:

- Calculate the difference between actual peak and trough concentrations measured in patient (D_m)

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT…

- Calculate the difference between peak and trough concentrations desired in that patient (D_d)

$$\text{The new dose required is} = \frac{D_m}{D_d} \times \text{old dose}$$

Step 2: Determine the New Dosing Interval:

- The dosing interval is estimated using the rough estimate of the half-life
- The peak concentration drops to trough concentration over a period of t_1 hours
- Find the number of half lives taken for drop in concentration from peak to trough

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT…

- The dosing interval is estimated using the rough estimate of the half-life
- The peak concentration drops to trough concentration over a period of t_1 hours
- Find the number of half lives taken for drop in concentration from peak to trough
- Divide t_1 by the number of half lives calculated above to get approximate number of half lives taken for drop in measured peak to trough concentration
- Similarly calculate the approximate number of half lives required for drop in desired peak to trough concentration

A SIMPLER APPROACH TO PHARMACOKINETIC DOSAGE ADJUSTMENT…

- Multiply the number of half lives taken for actual drop from peak to trough with desired one
- The result should be rounder off to the nearest practical time interval for dosing

Exercise:

Consider a patient who is receiving 100 mg of a drug every 8 hours and the measured peak and trough steady state concentrations are 8.6 and 1.4 mg/L, respectively. Assume the desired peak and trough concentrations are 30 and 1 mg/L. Calculate the dose and dosage interval to achieve the desired concentrations.

CALCULATING DOSAGE

Oral Drugs:

- Frequently, tablets or capsules for oral administration are not available in the exact dose that has been ordered
- In these situations, we must calculate the number of tablets or capsules that should be given to make up the ordered dose
- The easiest way to determine this is to set up a ratio and proportion equation
- The ratio containing the two known equivalent amounts is put on one side of the equation, and the ratio containing the unknown value is put on the other side
- The known equivalent is the amount of drug available in one tablet or capsule; the unknown is the number of tablets or capsules that are needed for the prescribed dose

$$\frac{\text{amount of drug available}}{\text{one tablet or capsule}} = \frac{\text{amount of drug prescribed}}{\text{number of tablets or capsules to give}}$$

CALCULATING DOSAGE

Oral Drugs:

- Sometimes the desired dose will be a fraction of a tablet or capsule, 1/2 or 1/4
- Some tablets come with score markings that allow them to be cut
- Pill cutters are readily available in most pharmacies to help patients cut tablets appropriately
- One must use caution when advising a patient to cut a tablet
- Many tablets today come in a matrix system that allows for slow and steady release of the active drug
- These drugs cannot be cut, crushed, or chewed
- A drug reference should always be consulted before cutting a tablet
- Capsules can be very difficult to divide precisely
- If the only way to deliver the correct dose to a patient is by cutting one of these preparations, a different drug or a different approach to treating the patient should be tried

CALCULATING DOSAGE – ORAL DOSAGE…

- Other oral drugs come in liquid preparations
- Many of the drugs used in pediatrics and for adults who might have difficulty in swallowing a pill or tablet are prepared in a liquid form
- The same principle used to determine the number of tablets needed to arrive at a prescribed dose can be used to determine the volume of liquid that will be required to administer the prescribed dose

$$\frac{\text{amount of drug available}}{\text{Volume available}} = \frac{\text{amount of drug prescribed}}{\text{volume to administer}}$$

- Even if you are working in an institution that provides unit-dose medications, practice your calculation skills occasionally to make sure that you can figure out the dose of a drug to give
- Power can be lost, computers can go down, and the ability to determine conversions is a skill that anyone who administers drugs should have in reserve

CALCULATING DOSAGE

Parenteral Drugs:

- All drugs administered parenterally must be administered in liquid form
- The person administering the drug needs to calculate the volume of the liquid that must be given to administer the prescribed dose
- The same formula can be used for this determination that was used for determining the dose of an oral liquid drug:

$$\frac{\text{amount of drug available}}{\text{Volume available}} = \frac{\text{amount of drug prescribed}}{\text{volume to administer}}$$

CALCULATING DOSAGE

Intravenous Solutions:

- Intravenous (IV) solutions are used to deliver a prescribed amount of fluid, electrolytes, vitamins, nutrients, or drugs directly into the bloodstream
- Although most institutions now use electronically monitored delivery systems, it is still important to be able to determine the amount of an IV solution that should be given using standard calculations
- Most IV delivery systems come with a standard control called a microdrip, by which each milliliter delivered contains 60 drops
- Macrodrip systems, which deliver 15 drops/mL, are also available; they are usually used when a large volume must be delivered quickly
- In giving IV drugs, the microdrip system is most commonly encountered
- Check the packaging of the IV tubing if you have any doubts or are unfamiliar with the packaging

CALCULATING DOSAGE – IV SOLUTIONS…

- The ratio that is used to determine how many drops of fluid to administer per minute is the following

$$\text{drops/minute} = \frac{\text{mL of solution prescribed per hour} \times \text{drops delivered per mL}}{\text{60 minutes/1 hour}}$$

- That is, the number of drops per minute, or the rate that you will set by adjusting the valve on the IV tubing, is equal to the amount of solution that has been prescribed per hour times the number of drops delivered per mL divided by 60 minutes in an hour

Exercise:

An order has been written for a patient to receive 400 mL of 5% dextrose in water over a period of 4 hours in a standard microdrip system (ie, 60 drops/mL). Calculate the correct setting (drops per minute)

PRECAUTIONS FOR DOSAGE CALCULATION

- One must know this acronym: **Please Excuse My Dear Arun Sir- PEMDAS**

- This acronym stands for the order of operation in which math calculations must be solved **(Parentheses, Exponents, Multiplication, Division, Addition, and then Subtraction)**

- If not performed in this order, the answer will be wrong

- We must ask several questions ourselves like,
  - What is being asked of me?
  - What do I need to solve for?
  - What units does my answer need to be expressed in?
  - What units do I need in my problem and what units to I need to get rid of?
  - Are there units in the problem that I need to convert in order to set up my problem? (we always want to work with similar units whenever possible)

PRECAUTIONS FOR DOSAGE CALCULATION

- What information in the problem do I need, and what information do I not need?
- How do I set up my problem to leave only the desired units in the answer?
- **Does my answer make sense? (very important)**

- We should be aware of different systems used in pharmaceutical calculations like, metric system, the apothecary system, the household system, and the avoirdupois system

- It is important to know how to convert dosages from one system to another by using conversion tables