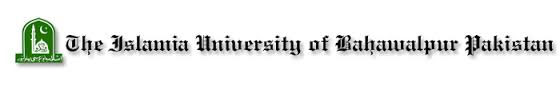
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**ASSIGENMENT:BIOPHARMACEUTICS**

**MULTIPLE-DOSAGE REGIMEN**

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FLOW IN PRESENTATION(topic):

1. ABOUT
2. DEFINATION
3. OBJECTIVE
4. PARAMETERS TO BE ADJUSTED
5. FACTORS TO BE CONSIDERED
6. DESIGN OF DOSAGE REGIMEN
7. PRINCIPLE OF SUPERPOSITION
8. DRUG ACCUMULATION
9. PLASMA PROFILE AFTER MULTIPLE DOSE REGIMENS
10. ACCUMULATION FACTOR
11. ACCUMULATION HALF LIFE
12. REPETIVE INTERAVENOUS INJECTIONS
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16. ADMINISTERING ONE OR MORE DOSES
17. MULTIPLE ORAL DOSE REGIMEN
18. LOADING DOSEDETERMINATION OF BIOAVAILABILITY AND BIOEQUIVALENCE
19. BIOEQUIVALENCE STUDIES
20. DOSE REGIMEN SCHEDULES
21. REFERANCE

1)ABOUT(WHY...) After single dose administration, the plasma drug level rises above and then falls below the minimum effective concentration (MEC), resulting in a decline in therapeutic effect. To maintain prolonged therapeutic activity, many drugs are given in a multiple dosage regimen.

2)ABOUT(WHAT…) An optimal dosage regimen is the one in which the drug is given in appropriate frequency which ensures maintenance of plasma drug concentration within the therapeutic window throughout the duration of therapy. Dosage regimen is the frequency of administration of a drug in a particular dose. It is also defined as the manner in which the drug is consumed. Should be convenient to the patient.

3)DEFINATION: Multiple-dosage regimen is the treatment of chronic diseases involving repeated administration dose at fixed interval to maintain the plasma concentration between minimum toxic concentration and maximum toxic concentration.

4)OBJECTIVE: The primary objective in the design of dosage regimen is to obtain a safe plasma drug concentration which neither exceeds the maximum safe concentration nor falls below the minimum effective concentration.

5)PARAMETERS: Dosage regimen is developed based on two parameters

1. Dose size of the drug

2. Frequency of administration (time interval between doses).

The two parameters are adjusted to have plasma concentration maintained in the therapeutic range especially for the narrow therapeutic index drugs.

6)FACTORS TO BE CONSIDERED:

Numerous factors must be considered in designing a dosage regimen.

* Pharmacokinetic factors:

these include( characteristics of a drug )

* + Absorption
  + Distribution
  + Metabolism‘
  + excretion
* PHYSIOLOGICAL FACTORS:

these include

* + Age
  + Weight
  + Gender
  + Nutritional status
* Pathophyiologic factors:

these include ( existence of disease like )

* + Renal failure
  + Hepatic disease
  + Heart disease
  + Lungs disease, etc..
* Personal life style:

habits like,

* + Cigarette smoking
  + Alcohol abuse
  + Voracious eating
* Exposure of patient to long term medication.
* Other factors:

these include,

* alteration in the sensitivity of the receptors to the drug
* Drug dosage form
* Drug interactions
* Tolerance dependence
* pharmacogenetics

7)DESIGN OF DOSAGE REGIMEN: Designing of dosage regimen for multiple dosing is mainly depends upon the following factors:

* Drug accumulation during multiple dosing of *i.v* bolus*.*
* Time taken to reach the steady state.
* Minimum and maximum concentration.
* Average concentration of the drug at steady state.
* Loading dose.
* Maintenance dose.

8)PRINCIPLE OF SUPERPOSITION: The principle of superposition allows one to project the plasma drug concentration–time curve of a drug after multiple consecutive doses based on the plasma drug concentration–time curve obtained after a single dose.

The basic assumptions are that

* The drug is eliminated by first-order kinetics
* The pharmacokinetics of the drug after a single dose (first dose) are not altered after taking multiple doses

According to this principle the next dose will overlay the plasma profile of the previous one. This helps in predicting the plasma concentration after multiple dosing.

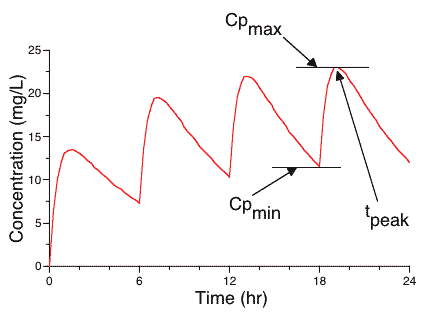
* There are situations, however, in which the superposition principle does not apply. In these cases, the pharmacokinetics of the drug change after multiple dosing due to various factors:
* Changing pathophysiology in the patient
* Saturation of a drug carrier system
* Enzyme induction
* Enzyme inhibition

Drugs that follow nonlinear pharmacokinetics generally do not have predictable plasma drug concentrations after multiple doses using the superposition principle.

9)DRUG ACCUMULATION: If the drug is administered at a fixed dose and a fixed dosage interval, as is the case with multiple-dose regimens, the amount of drug in the body will increase and until a plateau is obtained that is steady state concentration. When the second dose is given after a time interval shorter than the time required for complete elimination of the previous dose, the resulting peak plasma concentration will be higher than after the first dose. This is termed as *drug accumulation.* However there will be no drug accumulation if the second dose is given after a time interval longer than the time required for complete elimination of the previous dose, drug will not accumulate.

10)PLASMA PROFILE AFTER MULTIPLE-DOSAGRE REGIMENS: Drug accumulation during multiple dosage regimen results in increasing drug concentration until a steady state is achieved. At steady state the plasma concentration fluctuates between the maximum concentration Cmax and minimum concentration Cmin. Once a steady state is achieved Cmax and Cmin are constant and remain unchanged from dose to dose. Cmax is an indicator of the drug toxicity and drug accumulation. Cmax at steady state Cssmax and Cmin at steady state Cssmin after IV administration are calculated as follows

|  |  |
| --- | --- |
| Css max = | D |
| Vd (1- e-kτ ) | |

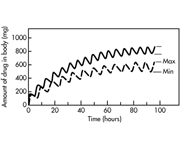


Cssmin = Css max e-kτ

And after oral administration

|  |  |
| --- | --- |
| Cmax = | FD |
| Vd (1-e-kτ) |

Css min = Cssmax. e-kτ

11)ACCUMULATION FACTOR: The Cssmax is also a good indication of drug accumulation. If a drug produces the same Cssmax at steady state, compared with the (Cn= 1) max after the first dose, then there is no drug accumulation. If C∞ max is much larger than (Cn = 1) max, then there is significant accumulation during the multiple-dosage regimen. Accumulation is affected by the elimination half-life of the drug and the dosing interval. The index for measuring drug accumulation *R* is

R= (Cssmax) / (Cn=1)

Substituting the value of Cssmax and Cn=1

R=1/ 1-e-kτ

Equation shows that drug accumulation measured with the *R* index depends on the elimination constant and the dosing interval and is independent of the dose. For a drug given in repetitive oral doses, the time required to reach steady state is dependent on the elimination half-life of the drug and is independent of the size of the dose, the length of the dosing interval, and the number of doses.

12)ACCUMULATTION HALF-LIFE:Equation for the estimation of the time to reach one-half of the steady-state plasma concentration or the accumulation half-life is described by Van Rossum and Tomey (1968).

Accumulation half life = t1/2 (1+3.3log ka/ ka -k)

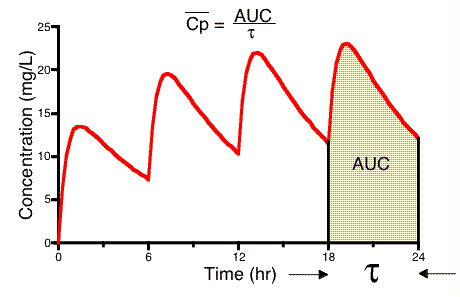
Where, ka = absorption rate constant and k = elimination rate constant

For IV administration, ka is very rapid (approaches ∞); k is very small in comparison to ka and can be omitted in the denominator of above Equation. Thus, the above equation reduces to

Accumulation half life= *t* 1/2(1+ 3.3logka/ ka)

The accumulation *t* 1/2 of a drug administered intravenously is the elimination *t* 1/2 of the drug. Thus, the time to reach 50% steady-state drug concentrations is dependent on the elimination *t* 1/2 and not on the dose or dosage interval.

Average plasma concentration at steady state

If the plasma profile is observed, it is noticed that Cmax,C min, Cssmax and Css min fluctuate around an average drug concentration. The average plasma concentration is not an average concentration of Cmax and C min. Average plasma concentration at steady state depends on the dosing rate and total body clearance and is given by

Cpss avg= FD/ CLT. Τ = AUC/ τ

Different dosage regimen may have same average plasma concentration if the bioavailability is same. For example consider following different regimens for same drug.

100 mg every 4 hr

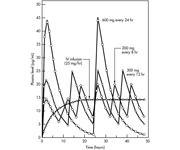
150 mg every 6 hr

200 mg every 8 hr

300 mg every 12 hr

The average plasma concentration will remain constant if the clearance remains constant. However this will result in different fluctuation around the average plasma concentration. So C max and C min will be different but C avg will be same.

13)REPETITIVE INTRAVENOUS INJECTIONS:The maximum amount of drug in the body following a single rapid

IV injection is equal to the dose of

the drug. For a one-compartment

open model, the drug will be

eliminated according to

first-order kinetics.



If τ is equal to the dosage interval, then the amount of drug remaining in the body after several hours can be determined with



The fraction (*f*) of the dose remaining in the body is related to the elimination constant (*k*) and the dosage interval (τ) as follows:

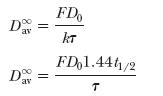


With any given dose, *f* depends on *k* and τ. If τ is large, *f* will be smaller because *D* B (the amount of drug remaining in the body) is smaller.

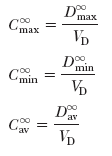
*D* ∞ max can be calculated directly by the relationship



The average amount of drug in the body at steady state, *D* ∞ av, can be found by following. *F* is the fraction of dose absorbed. For an IV injection, *F* is equal to 1.0.



The concentration of drug in the body after multiple doses is obtained by dividing the amount of drug in the body by the volume in which it is dissolved. For a one-compartment model, the maximum, minimum, and steady-state concentrations of drug in the plasma are found by the following equations:

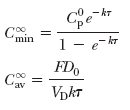


A more direct approach to finding *C* ∞ max, *C* ∞ min, and *C* ∞ av is





where *C* 0 p is equal to *D* 0/*V* D.

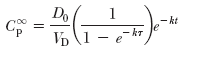


It is sometimes desirable to know the plasma drug concentration at any time after the administration of *n* doses of drug. The general expression for calculating this plasma drug concentration is

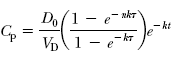


Where *n* is the number of doses given and *t* is the time after the *n*th dose.

At steady state, *e* – *nk* τ  approaches zero and Equation reduces to



14)PROBLEM OF A MISSED DOSE: The equation describes the plasma drug concentration t hours after the nth dose was administered; the doses are administered τ hours apart according to a multiple-dose regimen:



This equation is designated as “1”.

Concentration contributed by the missing dose is



This equation is designated as “2” in which *t* miss = time elapsed since the scheduled dose was missed. Subtracting Equation “2” from Equation “1” corrects for the missing dose as shown in Equation “3”.



*Note:* If steady state is reached (i.e. either *n* = large or after many doses), the equation simplifies to Equation “4”. Equation “4” is useful when steady state is reached.



Generally, if the missing dose is recent, it will affect the present drug level more. If the missing dose is several half-lives later (>5*t* 1/2), the missing dose may be omitted because it will be very

small. Equation “3” accounts for one missing dose, but several missing doses can be subtracted in a similar way if necessary.

15)EARLY OR LATE DOSE ADMINISTRATION DURING MULTIPLE DOSING: When one of the drug doses is taken earlier or later than scheduled, the resulting plasma drug concentration can still be calculated based on the principle of superposition. The dose can be treated as missing, with the late or early dose added back to take into account the actual time of dosing, using Equation “5”.



in which *t* miss = time elapsed since the dose (late or early) is scheduled, and *t* actual = time elapsed since the dose (late or early) is actually taken. Using a similar approach, a second missed dose can be subtracted from Equation “1”. Similarly, a second late/early dose may be corrected by subtracting the scheduled dose followed by adding the actual dose. Similarly, if a different dose is given, the regular dose may be subtracted and the new dose added back.

16)INTERMITTENT INTRAVENOUS INFUSION: Intermittent IV infusion is a method of successive short IV drug infusions in which the drug is given by IV infusion for a short period of time followed by a drug elimination period, then followed by another short IV infusion. In drug regimens involving short IV infusion, the drug may not reach steady state.

The rational for intermittent IV infusion is to prevent transient high drug concentrations and accompanying side effects.

Many drugs are better tolerated when infused slowly over time compared to IV bolus dosing.

ADMINISTERING ONE OR MORE DOSES BY CONSTANT INFUSION: SUPERPOSITION OF SEVERAL IV INFUSION DOSES:

For a continuous IV infusion



Equation may be modified to determine drug concentration after one or more short IV infusions for a specified time period.



Where, *R* = rate of infusion = *D*/*t* inf, *D* = size of infusion dose, and *t* inf = infusion period.

After the infusion is stopped, the drug concentration post-IV infusion is obtained using the first-order equation for drug elimination:



Where, *C* stop = concentration when infusion stops, *t* = time elapsed since infusion stopped

17)MULTIPLE-ORAL-DOSE REGIMEN: The above given figures present typical cumulation curves for the concentration of drug in the body after multiple oral doses given at a constant dosage interval. The plasma concentration at any time during an oral or extra-vascular multiple-dose regimen, assuming a one-compartment model and constant doses and dose interval, can be determined as follows:



This equation is designated as equation “6”.

Where, *n* = number of doses, *F* = fraction of dose absorbed, and *t* = time after administration of *n* doses.

The mean plasma level at steady state, *C*∞av, is determined by a similar method to that employed for repeat IV injections. This equation can be used for finding *C*∞av for any route of administration.



This equation shows that the magnitude of *C*∞av is directly proportional to the size of the dose and the extent of drug absorbed. Furthermore, if the dosage interval is shortened, then the value for *C*∞av will increase. The *C*∞av will be predictably higher for drugs distributed in a small *V* D (e.g. plasma water) or that have long elimination half-lives than for drugs distributed in a large *V* D (e.g. total body water) or that have very short elimination half-lives. Because body clearance (*Cl* T) is equal to *kV* D, substitution into the above equation yields.



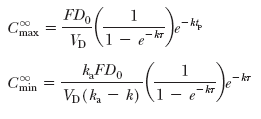
Thus, if *Cl* T decreases, *C*∞av will increase.

The *C*∞av does not give information concerning the fluctuations in plasma concentration (*C*∞max and *C*∞min). In multiple-dose regimens, *C*p at any time can be obtained using equation “6” where *n* = *n*th dose. At steady state, the drug concentration can be determined by letting *n* equal infinity. Therefore, *e – nk* becomes approximately equal to zero and Equation “1” becomes

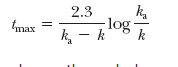


This equation is designated as equation “7”.

The maximum and minimum drug concentrations (*C* ∞ max and *C* ∞ min) can be obtained with the following equations:



The time at which maximum (peak) plasma concentration (or *t* max) occurs following a single oral dose is



Whereas, the peak plasma concentration is at *t* p, following multiple doses is given by Equation.

Large fluctuations between *C*∞max and *C*∞min can be hazardous, particularly with drugs that have a narrow therapeutic index. The larger the number of divided doses, the smaller the fluctuations in the plasma drug concentrations. For example, a 500-mg dose of drug given every 6 hours will produce the same *C*∞av value as a 250-mg dose of the same drug given every 3 hours, while the *C*∞max and *C*∞min fluctuations for the latter dose will be decreased by one-half. With drugs that have a narrow therapeutic index, the dosage interval should not be longer than the elimination half-life.

18)LOADING DOSE: Since extra-vascular doses require time for absorption into the plasma to occur, therapeutic effects are delayed until sufficient plasma concentrations are achieved. To reduce the onset time of the drug that is, the time it takes to achieve the minimum effective concentration (assumed to be equivalent to the *C*∞av)—a loading (priming) or initial dose of drug is given. The main objective of the loading dose is to achieve desired plasma concentrations, *C*∞av, as quickly as possible. If the drug follows one-compartment pharmacokinetics, then in theory, steady state is also achieved immediately following the loading dose. Thereafter, a maintenance dose is given to maintain *C*∞av and steady state so that the therapeutic effect is also maintained. In practice, a loading dose may be given as a bolus dose or a short-term loading IV infusion.

As discussed earlier, the time required for the drug to accumulate to a steady-state plasma level is dependent mainly on its elimination half-life. The time needed to reach 90% of *C*∞av is approximately 3.3 half-lives, and the time required to reach 99% of *C*∞av is equal to approximately 6.6 half-lives. For a drug with a half-life of 4 hours, it will take approximately 13 and 26 hours to reach 90% and 99% of *C* ∞av, respectively.

For drugs absorbed rapidly in relation to elimination (*k* a >> *k*) and are distributed rapidly, the loading dose *D* L can be calculated as follows:



This equation is designated as equation “8”.For extremely rapid absorption, as when the product of *k*a is large or in the case of IV infusion, *e* –*k*a becomes approximately zero and Equation “8” reduces to



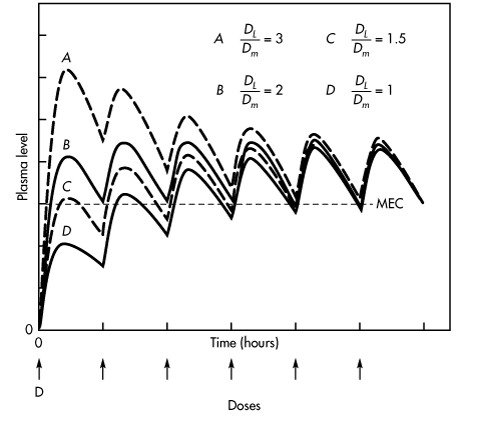
The loading dose should approximate the amount of drug contained in the body at steady state. The dose ratio is equal to the loading dose divided by the maintenance dose.



As a general rule, the dose ratio should be equal to 2.0 if the selected dosage interval is equal to the elimination half-life shows the plasma level–time curve for dosage regimens with equal maintenance doses but different loading doses. A rapid approximation of loading dose, *D* L, may be estimated from



This equation is designated as equation “9”. Where *C* ∞ av is the desired plasma drug concentration, *S* is the salt form of the drug, and *F* is the fraction of drug bioavailability.



Equation “9” assumes very rapid drug absorption from an immediate-release dosage form. The *D* L calculated by this method has been used in clinical situations for which only an approximation of the *D* L is needed.

These calculations for loading doses are not applicable to drugs that demonstrate multi-compartment kinetics. Such drugs distribute slowly into extra-vascular tissues, and drug equilibration and steady state may not occur until after the apparent plateau is reached in the vascular (central) compartment.

19)DETERMINATION OF BIOAVAILABILITY AND BIOEQUIVALENCE IN A MULTIPLE-DOSE REGIMEN: Bioavailability may be determined during a multiple-dose regimen only after a steady-state plasma drug level has been reached. The time needed to reach the steady-state plasma level is related to the elimination half-life, *t* 1/2, of the drug. As observed in, it takes approximately 6.6 half-lives to reach 99% of the *C* ∞ av.

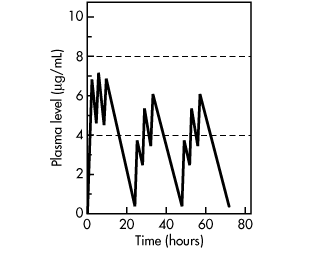
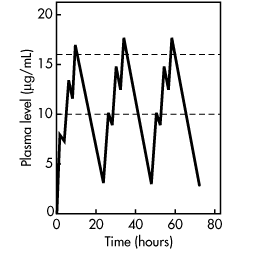
The parameters for bioavailability of a drug using plasma-level data from a multiple-dose regimen are similar to those obtained with a single-dose regimen. In the former case, the first plasma samples are taken just before the second dose of the drug. Thereafter, plasma samples are taken periodically after the dose is administered, in order to describe the entire plasma level–time curve adequately. Parameters including AUC, time for peak drug concentration, and peak drug concentration are then used to describe the bioavailability of the drug.

The extent of bioavailability, measured by assuming the [AUC]∞0, is dependent on clearance:



20)BIOEQUIVALENCE STUDIES: Pharmacokinetic analysis includes calculation for each subject of the steady-state area under the curve (AUC0–t), *t* max, *C* min, *C* max, and the percent fluctuation [100(*C* max – *C* min)/*C* min]. The data are analyzed statistically using analysis of variance (ANOVA) on the log-transformed AUC and *C* max. To establish bioequivalence, the AUC and *C* max parameters for the test (generic) product should be within 80–125% of the reference product using a 90% confidence interval.

21)DOSAGE REGIMEN SCHEDULES: Predictions of steady-state plasma drug concentrations usually assume the drug is given at a constant dosage interval throughout a 24-hour day. Very often however the drug is given only during the waking hours. Niebergall and associates (1974) discussed the problem of scheduling dosage regimens and particularly warned against improper timing of the drug dosage. For example, shows the plasma levels of Theophylline given three times a day. Notice the large fluctuation between the maximum and minimum plasma levels. In comparison, Procainamide was given on a 0.5-g, four-times-a-day maintenance dosage with a 1.0-g loading dose on the first day. However, on the second and third days, plasma levels did not reach the therapeutic range until after the second dose of drug.



Ideally, drug doses should be given at evenly spaced intervals. However, to improve patient compliance, dosage regimens may be designed to fit with the lifestyle of the patient. For example, the patient is directed to take a drug such as amoxicillin four times a day (QID) before meals and at bedtime, for a systemic infection. This dosage regimen will produce unequal dosage intervals during the day because the patient takes the drug before breakfast, at 0800 hours (8 AM), before lunch, at 1200 hours (12 noon), before dinner, at 1800 hours (6 PM), and before bedtime, at 2300 hours (11 PM). For these drugs, evenly spaced dosage intervals are not that critical to the effectiveness of the antibiotic as long as the plasma drug concentrations are maintained above the *minimum inhibitory concentration* (MIC) for the microorganism.

Patient compliance to multiple dose regimens may be a problem for the patient in following the prescribed dosage regimen. Occasionally, a patient may miss taking the drug dose at the prescribed dosage interval. For drugs with long elimination half-lives (e.g. levothyroxine sodium or oral contraceptives), the consequences of one missed dose are minimal, since only a small fraction of drug is lost between daily dosing intervals. The patient should either take the next drug dose as soon as the patient remembers or continue the dosing schedule starting at the next prescribed dosing period. If it is almost time for the next dose, then the skipped dose should not be taken and the regular dosing schedule should be maintained. Generally, the patient should not double the dose of the medication. For specific drug information on missed doses, USP DI II, *Advice for the Patient*, published annually by the United States Pharmacopeia, is a good source of information.

The problems of widely fluctuating plasma drug concentrations may be prevented by using a controlled-release formulation of the drug, or a drug in the same therapeutic class that has a long elimination half-life. The use of extended-release dosage forms allows for less frequent dosing and prevents under-medication between the last evening dose and the first morning dose. Extended-release drug products may improve patient compliance by decreasing the number of doses within a 24-hour period that the patient needs to take. Patients generally show better compliance with a twice-a-day (BID) dosage regimen compared to a three-times-a-day (TID) dosage schedule.

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* Basic pharmacokinetics by **Mohsin A. Hedaya**.
* Applied biopharmaceutics and pharmacokinetics by **Leon Shargel**.
* Modern pharmaceutics by **Gilbert S. Banker**.
* Basic pharmacokinetics and pharmacodynamics by **Sara E. Rosenbaum**.