BIOAVIALABILITY AND BIOEQUIVALENCE STUDIES

Dr. M.Mothilal
Assistant professor

INTRODUCTION:

- Bioavailability is a measurement of the rate and extent of drug that reaches the systemic circulation from a drug product or a dosage form .
- There are two different types of bioavailability studies:

1. First type involves an assessment of the bioavailability of new drug formulation ,pharmacokinetic parameters following different routes of administration of the new drug are obtained and are utilized in developing an optimum dosage regimen .
2. Second type is comparison of a test formulation with that of reference standard dosage form that is proved to have therapeutic efficacy and safety is known as bioequivalence studies

BIOAVAILABILITY STUDY PROTOCOL

The aim of bioavailability study is to find out the dosage form influence on the biological performance of the drug, sensitivity to detect differences in the rate and extent of absorption.

- STUDY OBJECTIVE
- STUDY DESIGN
- METHODS OF ASSESEMENT OF BIOAVAILABILITY
  - PLASMA DATA AND URINE DATA
  - ACUTE PHARMACOLOGICAL EFFECT AND CLINICAL RESPONSE.
- ANALYSIS AND PRESENTATION OF DATA.

STUDY OBJECTIVE

- A study design meant for estimating essential pharmacokinetic parameters differs significantly from a bioequivalence study meant for comparing the test formulation with reference to a standard.

- Factors have to be considered in conducting a bioavailability study are

  rate and extent of absorption of a drug in to the systemic circulation

- Distribution and elimination are influenced by variety of factors

- Subject factors such as age, sex, disease state, food habits, body weight ,time of administration and sampling, analytical method

  and compartment model used in P.K-parameters.

Cross-over design

- The cross over design is preferred in Bioavailability and bioequivalence trials to avoid influence of a inter-subject variation. Two types of cross over design is are used in bioavailability trials:

  Latin square cross-over design and

  balanced incomplete block design (BIBD)

- This design has several advantages:

  It minimizes the effect of inter-subject variability in the study

  it minimizes the carry over effects, minimizes the time effect

  on bioavailability ,it requires less number of subjects to get results.

Two-way crossover

Group no	Subjects in group	Treatment for period no	
		I	II
1.	1,2,3,4,5,6	A	B
2	7,8,9,10,11,12	B	A

Three-way cross over

Group no	Subjects in group	Treatment for period no		
		I	II	III
1.	1,2,3,4,5,6	A	C	B
2.	7,8,9,10,11,12	B	A	C
3.	13,14,15,16,17,18	C	B	A

Four-way cross over

Group no	Subjects in group	Treatment for period no			
		I	II	III	IV
1.	1,2,3,4,5,6	A	B	C	D
2.	7,8,9,10,11,12	B	D	A	C
3.	13,14,15,16,17,18	C	A	D	B
4.	19,20,21,22,23,24	D	C	B	A

WASH OUT PERIOD

- The time interval between the two treatment is called "washout period" is required for the elimination of the administered doses of a drug so as to avoid the carryover.

- Washout period is a function of the half-life and the dose of the drug administered, the number of washout period in a study depends on type of cross-over design used and the number of formulations to be evaluated , large number of drugs have been found to have half life between 1 and 10 ,a washout period of 1 week was usually found suitable in most of the reported studies

DRUG PRODUCTS:

- TEST PRODUCTS:

  The test products may be new drug formulations developed

  By a pharmaceutical technologist or new dosage forms of an existing drug, reasons for evaluation are:

  To select best dosage form of a new or existing drug

  select the best formulation of a new or existing drug, compare the biological performance of a test product to that of a recognized standard.

- REFERENCE STANDARD:

  generic product has to be compared with some standard dosage form to verify its in vivo performance .FDA accepts any innovators drug product as a reference standard

SAMPLING

- The sampling scheme should be frequent enough to define the absorption phase, and the elimination phase during a time course in the body.
- In order to estimate the rate of absorption it is necessary to have a enough data points in the absorption phase, the relative amount of drug absorbed is determined by AUC parameter

  sufficient sampling point to allow for proper evaluation.
- The AUC from the data , sampling has to carried out till the

  Concentration of the drug reaches the linear elimination phase
- A rule of thumb sampling in a blood level study is to sample for three to five half life's of the drug, if the half life is not known
- Sampling should proceed until 1/10 or 1/20 of the peak levels reached

IN THE CASE OF URINARY EXCRETION STUDIES ,THE SAME PRINCIPLES APPLY:

ADVANTAGES

- It involves non invasive method of sampling.
- The concentration of the drug in the urine is often greater than that in blood /serum allowing easy estimation of drug.
- The amount of the drug excreted in urine is obtained directly.

DISADVANTAGES

- Urinary studies are not useful in estimating the absorption

  rate of rapidly absorbing drug.
- The metabolites of the drug are also concentrated in the sample interfere with the estimation of the unchanged drug in the urine sample , urine samples should be collected for 10

  half lives of the drug to ensure a 99.9% of elimination of drug.

SELECTION OF SUBJECTS:

- Healthy volunteers should be used in bioavailability studies

- What is healthy volunteers?
- Healthy means a person having an overall good state of physical health. It is ascertained by vital signs such as temperature, pulse, respiration, blood pressure, and laboratory tests on blood

  and also by liver function test such as serum alkaline phosphates and serum glutamic - oxalacetictransaminase, depending upon the drug products used in the study.
- Age , sex and body weight also influence the blood level profile
- In generally acceptable normal ranges are 20 -50 years of age

  and 120 to 200 lb of body weight, males are preferred over females
- Selected subjects should be maintained on a uniform diet should

  not taken any drug at least one week prior to the study.

ANALYSIS OF BIOLOGICAL SAMPLES

- The biological samples collected as per the sampling procedure
  have to be analyzed immediately.
- The storage of biological samples as important aspect in a B.A
  study, since during storage the sample may undergo chemical
  degradation , adsorbtion on to the walls of the container etc.
- Analytical method must be selective and sensitive.
- Non specific analytical methods measuring a mixture of the unchanged drug and metabolites are less desirable even in well Controlled cross- over studies.
- Results obtained with one analytical method in one study should
  not be compared with those obtained in a other study with a different analytical method.

Methods of assessment of bioavailability

- The methods available are classified as pharmacokinetic methods and pharmacodynamic methods.
- Indirect methods of pharmacokinetic methods:
- The parameters are:

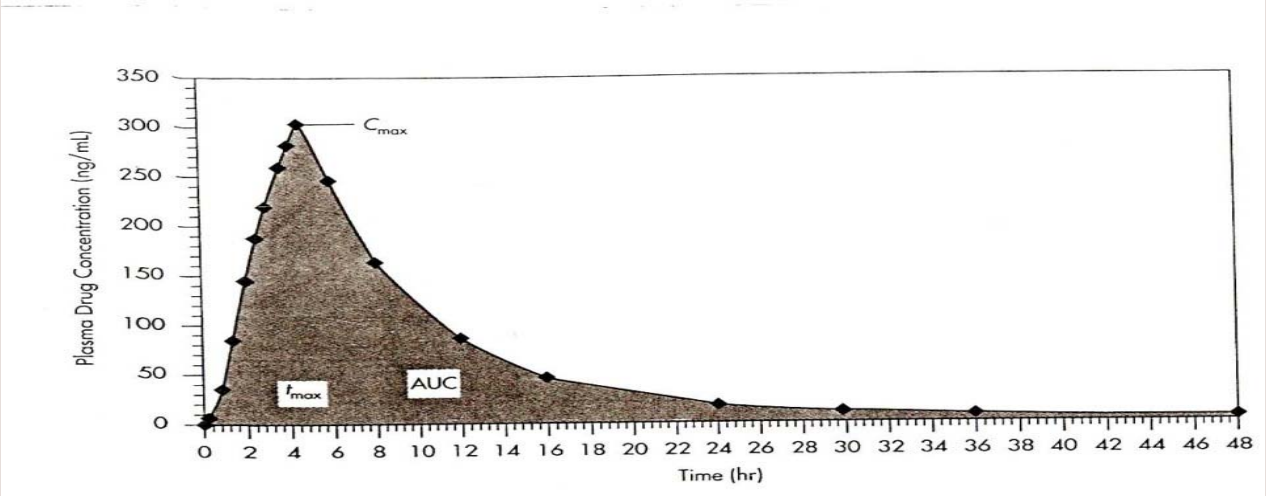
1. Plasma data

- The time of peak plasma concentration (t p)
- The peak plasma concentration (c max)
- The area under the plasma concentration – time curve (Auc)

2. Urine data:

- The rate of drug excretion in the urine (d x u/ dt)
- The cumulative amount of drug excreted in the urine (x u∞)
- The time for maximum urinary excretion (t u ∞)

PLASMA DRUG CONCENTRATION – TIME CURVE



ABSOLUTE BIO-AVAILABILITY

$$F = \frac{\text{(Auc) oral x dose IV}}{\text{(AUC) IV X DOSE ORAL}}$$

RELATIVE- BIO AVAILABILITY

$$Fr = \frac{\text{(AUC) TEST XDOSE STD}}{\text{(AUC) STD X DOSE TEST}}$$

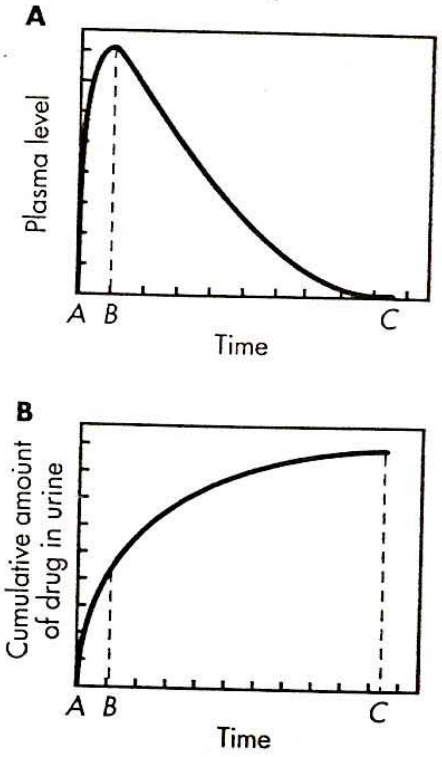


Figure 15-6. Corresponding plots relating the plasma level–time curve and the cumulative urinary drug excretion.

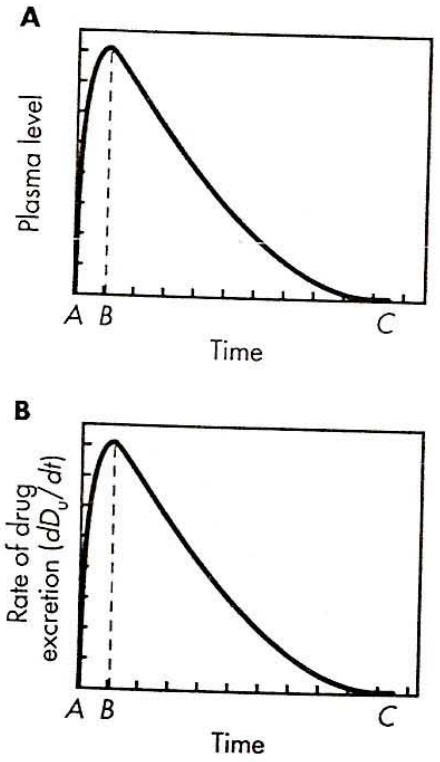


Figure 15-7. Corresponding plots relating the plasma level–time curve and the rate of urinary drug excretion.

DIRECT METHODS ORPHARMACODYNAMIC METHODS

- There are two pharmacodynamic methods used for the estimation of bioavailability
  - Acute pharmacological effect
  - Clinical response
- Measurement of acute pharmacological effect

1. An established dose- related response curve
2. An easily measurable pharmacological response such as heart rate, ECG , blood pressure, pupil diameter, etc.

a plot of observed pharmacological effect vs time is made in order to get a smooth curve

The area under this curve is used for estimation of bioavailability

CLINICAL RESPONSE

- Theoretically , this method seems to be the best among the methods , but practically it is not because of the fact that
- Differences in clinical response may be due to differences both in the pharmacokinectic and pharmacodynamic behavior of the drug among individuals ,the drug may be available to systemic circulation from a drug product at a sufficient rate and extent

  but may not elicit a clinical response in an individual because

  his receptors are less sensitive to drugs compared to others
- Various other factors include age, drug tolerance, drug interactions and unknown pathophysiological factors,in addition

  quantification of clinical response is too in accurate to be useful

  in assessment of bioavailability of drug products.

STATISTICAL ANALYSIS OF DATA

- The purpose of bioavailability study is to find out whether the test product is bioequivalent to standard product or not
- Due to biological and experimental variations ,some differences

  always exists .
- Statistical methods are used to evaluate the data in order to identify the different sources of variation and identify the variable and isolate the specific observation .
- The analysis of variance (ANOVA) , a statistical procedure

  used for cross over design , is widely used In bioavailability testing .