BIOAVAILABILITY & BIOEQUIVALENCE TESTING PROTOCOL

SRM UNIVERSITY
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Bioavailability

Def: Bioavailability is a measurement of rate and extent of active drug that reaches the systemic circulation and available at the site of action.

Bioequivalence

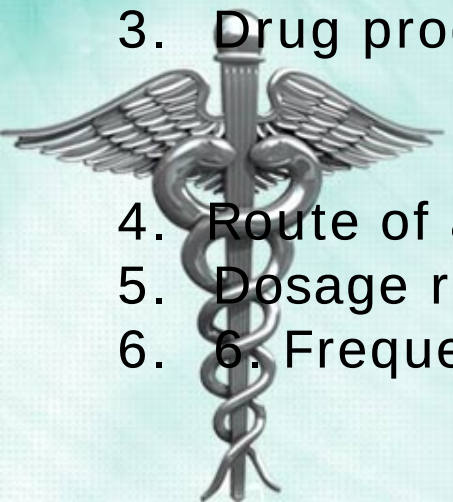
Def: It refers to a procedure that compares the bioavailability of a drug from different formulations.

- The aim of bioavailability study is to find out the dosage form influence on the biological performance of the drug.

- The bioavailability study protocol used to detect differences in the rate and extent of absorption that are attributable only to dosage form variability and should avoid variabilities due to other factors.

- **Bioavailability study protocol divided into**

A. Study objective
B. Study design
    1. Experimental design
    2. Wash out period
    3. Drug products
        I. Test product
        II.Recognized standard
    4. Route of administration
    5. Dosage regimen
    6. 6. Frequency and duration of sampling



7. Randomization of drug administration
8. Single-versus multiple-dose study design
9. Subjects
    I. Healthy subjects versus patients
    II. Subject selection
        a. Medical history
        b. Physical examination
        c. Laboratory tests
    III. Study conditions
10. Analysis of biological fluids

C. Methods of Assessment of Bioavailability

1. Plasma data
2. Urine data
3. Acute pharmacological effect
4. Clinical response

D. Analysis and Presentation of Data

1. Statistical treatment of data-Analysis of variance (ANOVA)
2. Format of data

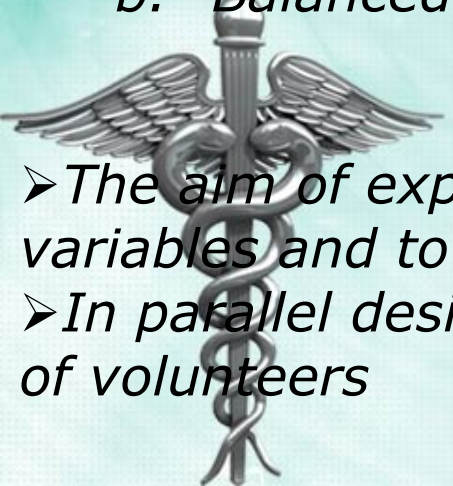
Study objective

- *Bioavailability studies are performed for new drugs to establish pharmacokinetic parameters including*
  - *Rate of absorption*
  - *Rate of excretion*
  - *Metabolism*
  - *Elimination*
  - *Half life of single and multiple dose administration*

Study design

Study design is two types

1. *Parallel design*
2. *Cross over design*
   a. *Latin square cross over design*
   b. *Balanced incomplete block design*



Parallel design

- *The aim of experimental design is to minimize the experimental variables and to avoid a bias.*
- *In parallel design two formulations are administered to two groups of volunteers*

Disadvantage

- *The intersubject variation is not being corrected.*

Cross over design

- *Minimizes the effect of intersubject variability in the study.*

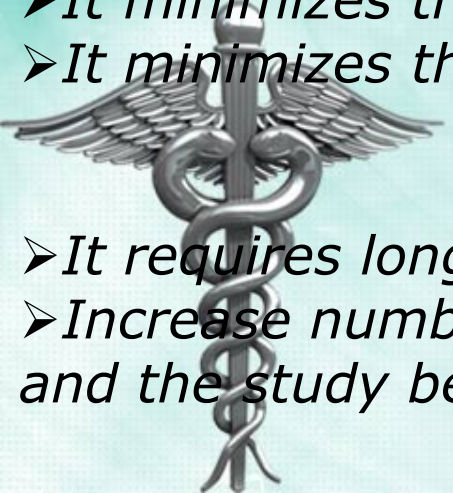
Latin square cross over design

In this design

- *Each subject receives just once each formulation.*
- *Each formulation is administered just once in each study period.*

Advantages

- *Minimize the effect of intersubject variability.*
- *It minimizes the carry over effects.*
- *It minimizes the time effect on bioavailability.*



Disadvantages

- *It requires longer time to complete the study.*
- *Increase number of study periods leads to high subject dropouts and the study becomes difficult.*

Balanced incomplete block design

The salient features of this design are

- Each subject receives not more than two formulations
- Each formulation is administered the same number of times

Washout period

- The time interval between the two treatments is called washout period.
- Washout period is required for the elimination of the administered dose of a drug.
- Washout period is a function of the half and dose of the drug administered.

E.g. digitoxin which has a half life of 6-9 days washout period.

Drug products

Test products:

Test products are generally evaluated for following reasons.

- To compare biological performance of a test product to that of a recognized standard i.e. bioequivalence studies.
- To select best dosage form of a new drug or existing drug among different dosage forms. E.g. tablet, capsule, emulsion and suspension.

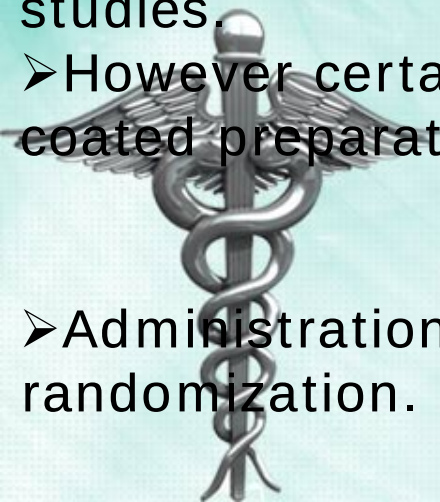
Route of administration

- Most of the times, orally administered dosage forms are subjected for bioavailability studies.
- Dosage forms administered by other routes (buccal, transdermal and intramuscular) should also be evaluated for their biological performance.

Single dose vs multiple dose study design

- Useful to know wheather a single dose studies are better or multiple dose studies are better for the assessment of the bioavailability of a drug product.
- If dosage forms are to be evaluated only for bioequivalence purposes, single dose studies are usually sufficient.

  E. g. analgesics for the relief of headache need only single dose studies.
- However certain dosage forms (time release products, enteric coated preparations) requires multiple dose studies.



Administration of drug products

- Administration of drug products to the subjects should be based on randomization.

- After the administration of the drug products, blood samples are withdrawn from the subjects at fixed time points. It takes some time to take a sample from each subject, and the total time difference between first subject and last subject may range from 10 to 20 minutes.
- This 10 to 20 minutes difference would represent a substantial change in the drug concentrations observed in the blood.

Sampling

- The sampling scheme should be frequent enough to define the absorption phase, the peak and elimination phase during a drug's time course in the body.
- To estimate the AUC from the data, sampling has to be carried out till the concentration of the drug reaches the linear elimination phase.

Selection of subjects

Healthy subjects vs patients:

- Use of healthy volunteers avoids much of variations that are possible with patients.
- Some of special problems associated with testing in patients are given below

1. It is difficult to obtain many patients in a given place.
2. The severity of a disease varies from one patient to another.

Study conditions

- The selected subject should be

1. Maintained on a uniform diet.
2. None of them should have taken any drug atleast one week prior to study.

- In general bioavailability trials are conducted on subjects that has fasted overnight.

Analysis of biological samples

- The biological samples collected as per the sampling procedure have to be analyzed immediately after the study.
- Analysis of biological samples are carried out by
  1. Analytical method
  2. Non specific analytical method

Methods of assessment of bioavailability

Two types

1. Pharmacokinetic methods (indirect methods)
2. Pharmacodynamic methods (direct methods)

Pharmacokinetic methods

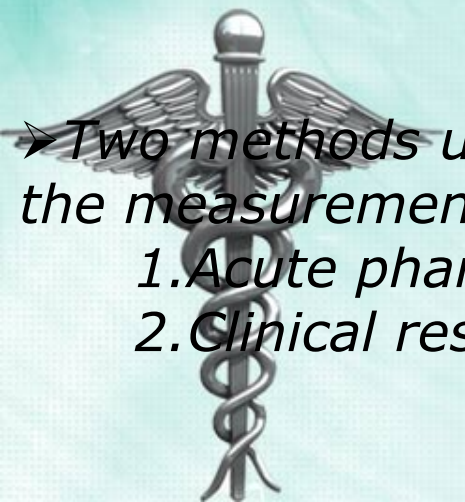
The parameters that are useful in determining the bioavailability of drug from a drug product based on indirect methods are

1.Plasma data

a. *Time of peak plasma concentration (t_p)*
b. *Peak plasma concentration (C_{max})*
c. *Area under the plasma concentration-time curve (AUC)*

2.Urine data

a. *The rate of drug excretion in the urine (dX_u/dt)*
b. *The cumulative amount of drug excreted in the urine (X_u^∞)*
c. *The time for maximum urinary excretion (t_u^∞)*



Pharmacodynamic methods

➢*Two methods used for the estimation of bioavailability are based on the measurement of*

1.Acute pharmacological effect
2.Clinical response

Statistical analysis of the data

- The purpose of a bioavailability test is to find out whether the test formulation gives a blood level profile identical to that observed for a reference standard product or not.

- Statistical methods are used to evaluate the data in order to identify the different sources of variation and if possible, to measure the contribution of each identified variable and isolate the specific observation of primary interest.

- The analysis of variance (ANOVA), a statistical procedure used for a cross over design, is used widely in bioavailability testing and is the procedure that will be encountered most frequently by the health scientist.

REFERENCE

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- Principles & Applications of Biopharmaceutics and Pharmacokinetics by Dr.H.P.Tipins, Pg.no: 163 – 169

- Biopharmaceutics and Pharmacokinetics by Brahmankar, Pg.no: 283