MEASUREMENT OF BIOAVAILABILITY

Presented by : SHIKHA SINGH
Under the guidance of :Dr Vamshi Krishna T
Department of Pharmaceutics
Registration No. 160617009

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INTRODUCTION

- **Bioavailability is defined as rate & extent of absorption of unchanged drug from its dosage form & become available at the site of action**
- **Bioavailability of a drug from its dosage form depends upon 3 major factors:**

- **pharmaceutical factors**
- **Patient related factors**
- **Route of administration**

OBJECTIVES

- Development of new formulations
- Determination of influence of excipients, patient related factors & possible interaction with other drugs on the efficiency of absorption
- Control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage, stability on drug absorption
- Primary stages of the development of a suitable dosage form for a new drug entity

ABSOLUTE BIOAVAILABILITY (F)

- When systemic availability of drug administered orally is determined in comparison to its intravenous administration is called absolute bioavailability

$$\text{ABSOLUTE BIOAVAILABILITY} = \frac{[AUC]oral\ (Dose)IV}{[AUC]IV\ (Dose)oral}$$

RELATIVE BIOAVAILABILITY (FR)

- When systemic availability of drug after oral administration is compared with that of an oral standard of same drug, it is referred to as relative bioavailability

$$\text{RELATIVE BIOAVAILABILITY} = \frac{[\text{AUC}]\text{Test (Dose)Std}}{[\text{AUC}]\text{Std (Dose)Test}}$$

METHODS OF ASSESSING BIOAVAILABILITY

PHARMACOKINETIC METHODS

- Plasma Level- Time Studies
- Urinary Excretion Studies

PHARMACODY NAMIC METHODS

- Acute pharmacological response
- Therapeutic response

PHARMACOKINETIC METHODS

1. Plasma level- time studies

- Most common type of human bioavailability studies
- Based on the assumption that there is a direct relationship between the concentration of drug in blood or plasma & concentration of drug at the site of action

SINGLE DOSE STUDY

Single Oral dose method

Collection of serial blood samples for a period of 2 to 3 biological half-lives after drug administration

Plot of concentration vs time to obtain the plasma level time profile

At least 3 points should be taken on the ascending part of the curve for accurate determination of ka

SINGLE DOSE STUDY

Single IV dose method

Sampling should start within 5 minutes of drug administration and subsequent samples taken at 15 minute intervals

Plot of concentration vs time to obtain the plasma level time profile

To describe disposition phase, atleast 3 sample points should be taken if the drug follows one-compartment kinetics & 5 to 6 points if it fits two-compartment model

MULTIPLE DOSE STUDY

Drug administration for at least 5 biological half-lives with a dosing interval equal to or greater than the biological half-life to reach the steady-state

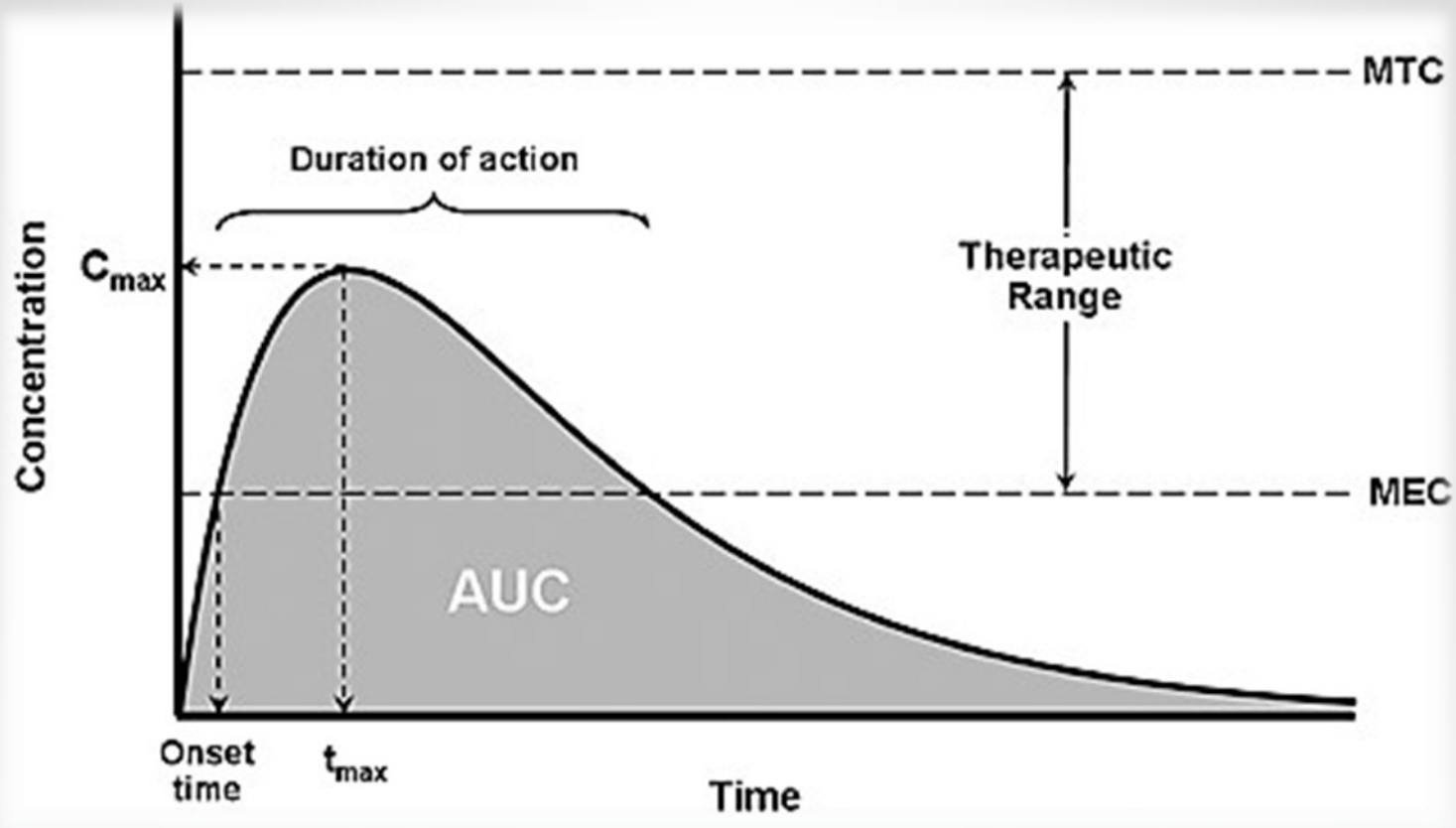
A blood sample should be taken at the end of previous dosing interval & 8 to 10 samples after the administration of next dose

BIOAVAILABILITY PARAMETERS

- **Bioavailability (the rate and extent of drug absorption) is generally assessed by the determination of following three parameters**

  - **C_{max} (*peak plasma concentration*)**
  - **T_{max} (*time of peak*)**
  - **Area under curve**

PLASMA DRUG CONCENTRATION- TIME PROFILE



- **C_{max} (Peak plasma drug concentration)**
  - Maximum concentration of the drug obtained after the administration of single dose of the drug
  - Expressed in terms of µg/ml or mg/ml
- **T_{max} (Time of peak plasma conc.)**
  - Time required to achieve peak concentration of the drug after administration
  - Gives indication of the rate of absorption
  - Expressed in terms of hours or minutes
- **AUC**
  - It is the measurement of the extent of the drug bioavailability

The extent of bioavailability can be determined by the following equations

- **FOR SINGLE DOSE STUDY:**

$$F = \frac{[AUC]\text{oral Div}}{[\text{AUC}]\text{iv Div}}$$

$$Fr = \frac{[AUC]\text{test Dstd}}{[\text{AUC}]\text{stdDtest}}$$

- **FOR MULTIPLE DOSE STUDY:**

$$Fr = \frac{[AUC]\text{test Dstd}\tau\text{test}}{[\text{AUC}]\text{stdDtest}\tau\text{std}}$$

$$Fr = \frac{(\text{Css, max})\text{test Dstd }\tau\text{test}}{[\text{Css, max}]\text{stdDtest}\tau\text{std}}$$

2. Urinary excretion studies

- Urinary excretion of unchanged drug is directly proportional to plasma concentration of drug
- Thus, even if a drug is excreted to some extent (at least 10 to 20%) in the urine, bioavailability can be determined
- Noninvasive method, so better patient compliance
- Eg: Thiazide diuretics, Sulphonamides

Method to estimate unchanged drug from urine sample

Collection of urine at regular intervals for a time span equal to 7 biological half-lives

Analysis of unchanged drug in the collected sample

Determination of the amount of drug excreted in each interval and cumulative amount excreted

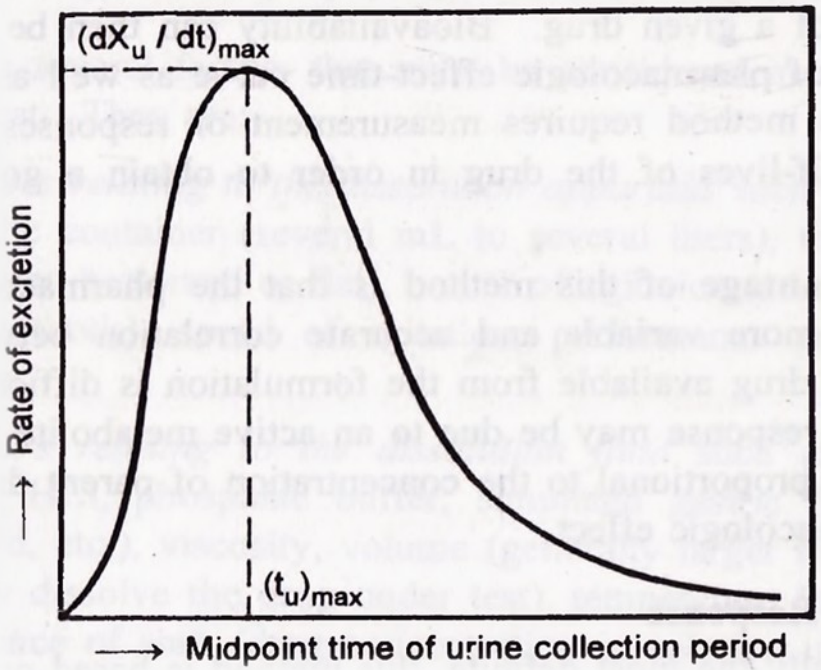
BIOAVAILABILITY PARAMETERS

- **Three important parameters in urine excretion data for single dose study:**

➢ $(dx_u/dt)_{max}$

➢ $(t_u)_{max}$

➢ x_u^{∞}



- **$(Dx_u/dt)_{max}$** (maximum urinary excretion rate)
  - Its value increases as rate and/or extent of absorption increases
  - Obtained from peak of plot between rate of excretion versus midpoint time of urine collection period
- **$(T_u)_{max}$**
  - Time for maximum excretion rate
  - Its value decreases as absorption rate increases
  - Analogues of t_{max} of plasma level data
- **X_u^∞**
  - Cumulative amount of drug excreted in urine
  - It increases as the extent of absorption increases

The extent of bioavailability can be determined by the following equations

- **FOR SINGLEDOSE STUDY:**

$$F = \frac{(Xu)\text{oral Div}}{(Xu)\text{iv Doral}}$$

$$Fr = \frac{(Xu)\text{test Dstd}}{(Xu)\text{std Dtest}}$$

- **FOR MULTIPLEDOSESTUDY:**

$$Fr = \frac{(Xu, ss)\text{test Dstd } \tau\text{test}}{(Xu, ss]\text{stdDtest}\tau\text{std}}$$

PHARMACODYNAMIC METHODS

1. Acute pharmacologic response method

- When bioavailability measurement by pharmacokinetic method is difficult, inaccurate or non-reproducible, an acute pharmacologic method is used
- Bioavailability can then be determined by construction of pharmacological effect- time curve as well as dose response graphs
- Method requires measurement of responses for at least 3 biological half-life of the drug in order to obtain a good estimate of AUC

2. Therapeutic response method

- This method based on observing the clinical response to a drug formulation given to patient suffering from disease
- A major drawback of this method is that quantitation of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug

CONCLUSION

- **Bioavailability is a key pharmacokinetic parameter which must be systematically estimated for a new drug formulation or a new modality of administration**
- **Bioavailability studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, manufacturing process of the drug product**

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Thank
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