Micro-dosing trials.

- Phase 0 clinical trials are also called as 'micro-dosing trials.'

- Study of new drug in micro doses to derive PK information. Before undertaking phase 1- studies is called Phase 0 trials.

- They are first CTs done among people.
- Aim to learn how a drug is processed in the body & how it affects the body.

- A very small dose of drug is given to 10 to 15 people.

- These studies aim to find if the drug behaves in the way researchers wants it to behave from their lab studies.

- Usually involves smaller no. of people and they have a very small dose of drug.

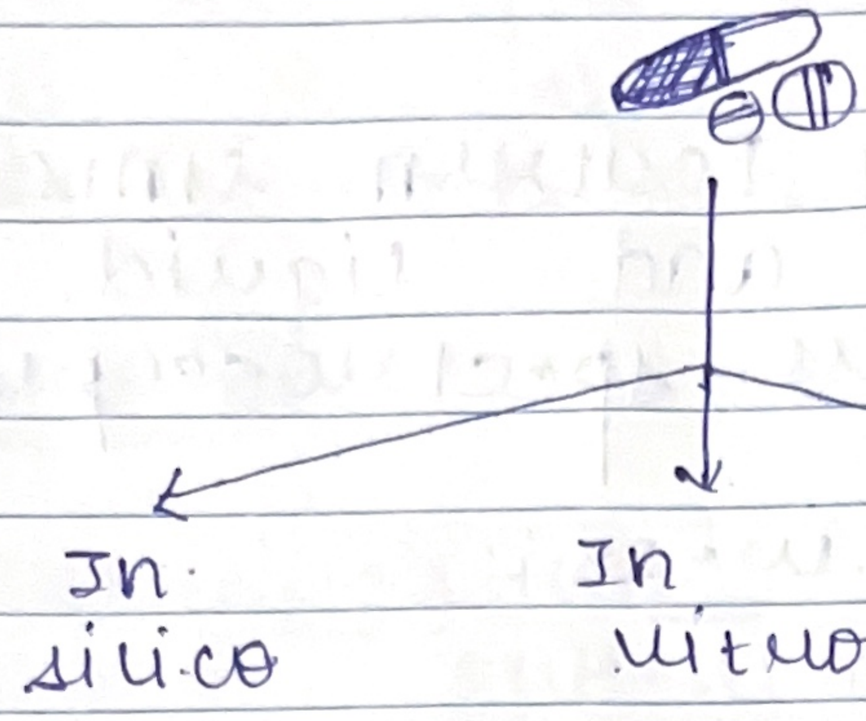
- Less than 1/100th of the dose is calculated to yeild a p'cological effect of the test drug based on primary PD data attained from in-vitro & invivo at a max dose of <100 mcg.

Procedures

In silico

- Plasm
c
- samp
m
- Mic

Procedure:



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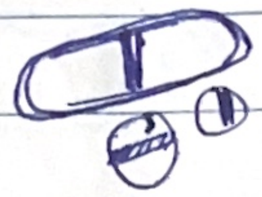

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Limited toxicology studies.

↓

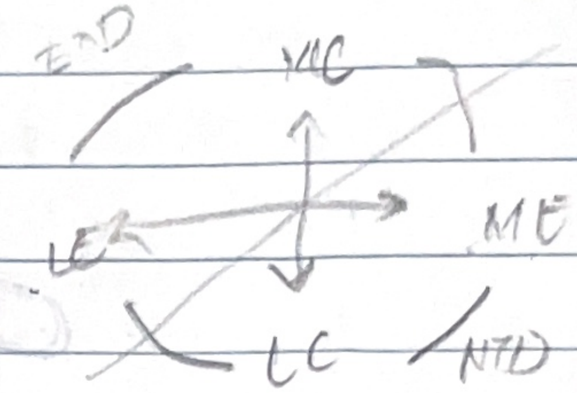
Human microdose study.
(Phase - 0).

- Plasma / urine / Biopsy samples are collected.
- samples analysed for parent drug & metabolite
- Micro dose → Micro. plasma drug conc.

- Extremely sensitive analytical methods are required.

Micro-dose is done by Positron emission Tomography (PET) and liquid chromatography Mass spectroscopy.

Advantages. → 1(a). W-22



Various phases of clinical trials.

- clinical trials are a systemic investigations done on human subjects for evaluating safety and efficacy of any new drug.

There are 4 different phases of clinical trials. They are:

(1) Phase - I clinical trial.

- Also known as 'Human P'cology and safety phase.'

(a) Objective: Determine, P'cological actions and tolerability

(b) FTBI : PD, PK, Tolerated dose
↙ ↘
(side effect) (ADME of drug)
on desired effect

(c) Data focus: Vital signs & plasma conc^{n}.

(d) Duration: Months.

(e) Population: Healthy volunteers / may be with target disease (cancer; TB etc.)

(f) Sample size: 20-80

(g) Type of study: Unblinded & Uncontrolled.

(2) Phase - II Clinical trial:

- Also known as 'Therapeutic exploration & dose-ranging'

(a) Objective: To Evaluate safety, efficacy, side effects, ADR.

(b) FTBI: Drug-drug & drug-disease interactions, PK & PD

(c) Data focus: Dose response & efficacy

(d) Duration: Several Months - Years.

(e) Population: Individuals & target disease

(f) Sample size: 200 - 300

(g) Type of study: May be Placebo, Active & controlled.

Phase - II

Phase IIa aimed to assess dosing requirements

Phase IIb specifically designed to study efficacy.

(3) Phase III clinical trials

- Also known as 'Therapeutic confirmatory trial.'

(a) Objective: Evaluate effectiveness and tolerability of the drug.

(b) FTBI: Dosage intervals, Risk - benefit information, safety & efficacy.

(c) Data focus: Late data & ADR.

(d) Duration: Several years.

(e) Population: Diverse population with target disease.

(f) Sample size: 300 - 1000

(g) Type of study: Randomized & controlled.

Phase - III

↙ Phase IIIa
To get sufficient & significant data

↘ Phase IIIb to show the drug work for additional types of patients.

(4) Phase IV clinical trials:

- Also known as 'Past Marketing Surveill -ance trial.'

(a) Objectives: Monitor long-term effects and effectiveness of the drug.

(b) FTBI: Epidemiological data, efficacy & safety, p'economics.

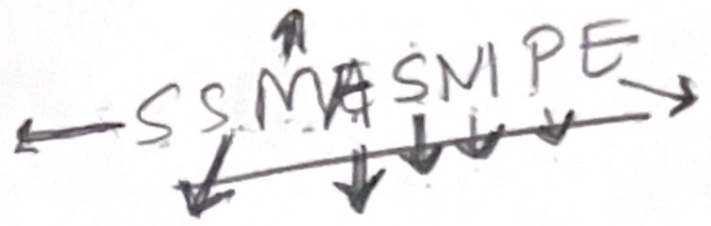
(c) Data focus: Efficacy, epidemiological data and economics

(d) Duration: Ongoing following FDA approval.

(e) Population: Diverse population with target disease & new age groups, gender.

(f) Sample size: More than 1000.

(g) Type of study: Expanded safety comparison



Drug characterization

- It involves the finding of the biological and physico-chemical properties of potential drug molecules.

⇒ Add table on Pg 31

It is of two types:

(1) Biological drug characterization:

- Assess whether the molecule will likely work in humans.

Eg: Receptor binding
Enzyme inhibition

Goals - To find efficacy
To assess toxic effects.

(a) cellular assays.

- Cellular cultures - cell penetration, receptor activity, transport

- Isolated tissues - Effects on specific tissue possible toxicity

- Liver tissues - Drug interaction and drug metabolism.

(b) Molecular assay
- MOA @ at molecular level
- Receptor binding assays (affinity and selectivity)

- Metabolic processing

(c) whole animal assays.

- Rat, mouse - Toxicity, LD50, organ specific toxicity

- Dog, rabbit, guinea, monkey - PK/PD, toxicity, bioavailability

- Can animal models for disease - Efficacy and toxicity

(2) Physico-chemical drug characterization

- These properties of a drug are crucial for knowing how it can be formulated or stored or administered.

(a) Solubility - → (S, LOGS)
- Ability of solute to dissolve in a solvent.

(b) PKa.-

- It is one method used to indicate the strength of an acid.

- It is the negative log of the acid dissociation constant or ka value.

(c) Partition coefficient -

- It is the ratio of concentrations of a compound in a mixture of two immiscible solvents at eqm.

(d) Stability -

- The stability of nano-medicines may be affected by one or more factors : Temp.
Moisture
Solvents
pH
particle size.
Exposure to diff types of ionizing & non-ionizing Radiation.

(e) chemical structure -

(i) Mass spectroscopy : Major analytical technique used to examine Mass, elemental compo & chemical struc. of a particle.

(ii) NMR: contrast to imaging & diffraction technique affording structural info at long-range order.

(iii) x-ray: Powerful technique.

↙ ↓ ↘

wide angle x-ray scattering

small angle x-ray scattering

ultra small angle x-ray scattering.

(iv) crystallography: Branch of science that deals with discerning the arrangement & bonding of atoms in crystalline solids.

(F) Impurities --

(i) TLC: used to seperate non-volatile mix. Performed on a sheet.
ex - glass, plastic, Al. foil.

(ii) HPLC: Form of column chromato. that pumps a sample mix or analyte in a solvent.

(iii) Mass spectrography: Used to determine the mass, elemental comp or chemical struc. of a particle or a molecule.

(Q) Polymorphism -

- ~~Use~~ Ability of an object to take on many forms.

- Use: Polymorphism in OOP occurs when a parent class reference is used to refer to child class object.