Pharmacology sheet #2

We will start to talk about preclinical studies of drug formation.

Preclinical studies including :
A) vitro studies (we use animal not human),vitro studies including :

1-) determine efficacy of the drug

2-) determine pharmacokinetic parameters ( like: absorption/metabolism…etc )

3-) determine pharmacodynamics

4-) assessment of drug toxicity ( safety of the drug )

b) acute toxicity studies : determination of LD50 and safety ,this studies are done on animals

c-) subacute and chronic toxicity studies : in this stage of preclinical studies we give a safe repeated dose for animals for one to two months and examining different organs ( daily observation ) .

d-) special toxicity studies : determination the mutagenicity of the drug

what is meaning of the mutagenicity of the drug ?

any substances in drug that can lead to congenital

malformation , this parameter has been determine before using the drug in human being , example ; bacterial mutagenicity test or administration of the drug to pregnant animal to know if this drug make any congenital malformation in fetus or not , and this test is done in vitro.

e-) carcinogenicity study : this test is done to know this drug could lead to cancer or not .

\*this test isn't necessary to do for all drugs .

For example ; if I have a drug highly efficacious , not toxic in acute and subacute and chronic studies , has a negative mutagenic effect , highly management of specific disease , we allow to marketing this drug ; after marketing if any patient suffers any problems ( have a cancer ) we throw this drug .
it isn't necessary to do this study if the drug excellent because this studies take 15-20 years .

If the drug has a positive mutagenic effect (it has a complete congenital malformation) or the chemical structure of the drug has a highly reactive substances ( toxicity group in the drug )in this case we should to do the carcinogenicity studies before using in human being .

Now we test the drug :is safe , is efficient , knowing the safe dose , no mutagenic effect ; now we start in clinical drug trials ( test the drug in human being ) but we have 4 phases of clinical drug studies .

Clinical drug studies :

Phase zero or subphase : doesn't assess a safety of the drug because we use micro doses ( subtheraptic dose ) .

\*small dose to assess pharmacokinetic and pharmacodynamics of the drug .

We give this small doses to 10-15 human subjects .

Phase zero giving an idea about the mechanism of the drug in human being including pharmacokinetics and pharmacodynamics and there is nothing to do with the safety .

Phase (1) :use drug to established dose level at which sign of toxicity first appear (assessment of safe dose ) , we give the dose to 20-80 healthy human subjects and observe if the side effect doesn't appear we increase the dose until the side effect appear .

\*phase 1 assess a safety as well as pharmacokinetic and pharmacodynamics.

This studies occur in hospital because the healthy subject maybe die from the side effect .

It must be healthy to assess the side effect of the drug .

Phase(2) : the drug is administered to patients for first time , and this phase occurs in hospital .

In phase 2 we prefer the patient has only one problem ( one disease ) to control our study .

This phase is assess efficacy and establishes optimal dose range in patients .

We take 50-300 patients and observe the toxicity of the side effect to assess safety of the drug.

Phase (3) :same phase 2 but more number of patients (one problem,one disease ) hundreds to thousands .

And also could detect another side effect , wasn't appeared in phase 2 .

Phase (4) (post marketing studies ): after phase 3 the drug was approved to be in market .

This phase is very essential because we give this drug to huge number of patients so we must observe this patient's.

In this phase we have 2 types of studies :

1-) controlled

2-) uncontrolled

In controlled studies we giving the drug to a certain number of patients , and giving same drug to other people called placebo .

Placebo : people who take the drug have everything like real drug except the active substance .

We will not observe any response to the drug in placebo .

In this phase we compared this drug with another drug used for same disease .

In uncontrolled studies we don't have placebo .

Single blind :examiner know the drug ,but the volunteer don't

Double blind :examiner + volunteer don't know the drug to eliminate a lot of variations specially in our countries .

Phase 4 assess safety and efficacy , and allow to discovering another target of this drug ex:

1-) aspirin was used as analgesic later on they discover ,aspirin can be used as antiplatelet protect us from myocardial infarction

2-)sildenafil citrate (Viagra) : was used as antihypertensive , is an excellent drug but they observed a lot of death they threw it from the market , and in one day someone asked about this drug because he was used to improved sexual function.

And after studying all patients was death the doctors discovered all patients was taking nitrate (nitrate major drug use for ischemic heart disease ) and they discovered Viagra + nitrate = death .

And now the Viagra is widely used because post marketing studies .

From slide 37-42 read it (el doctor ma shar7hom bas mar2 3alihom bsor3a )

Dosage forms of drugs

A chemical nature of the drugs :

Most of the drugs are either weak acids or weak bases exist in biological system either ionized or non-ionized .

Acidic like aspirin

Basic like morphine

Neutral like steroids

Sources of drugs :

1-) natural :

Plants :( atropine , digoxin )

Animals: (insulin) like pigs and cows insulin .

Humans: (growth hormone ) (hMG; human menopausal gonadotropin) (hCG; human chronic gonadotropin ) ,hMG after menopause, the women stop use estrogen , the body eliminate estrogen by throw it in urine, we isolate estrogen from urine .

2-) semisynthetic : ( human insulin ) this source is between natural and synthetic ; the source from nature but we do some modification . like human insulin we took the pigs insulin (1 A.A different from human ) or cows insulin (3A.A different from human ) and doing some modification .

3-)synthetic :now days after understanding chemical structure we can synthesis any drug ( agonist ) or (antagonist) .

Naming drugs :

Drug has many names :

1-) chemical name :hardly to use, based on chemical structure ( ex: acetyl salicylic acid )

2-) generic name : easy to use , most widely used name (ex: aspirin)

3-)official name : the name after approval( asprin**BP** , aspirin **USP**) .

4-)trade name : the name which is a signed by the manufacturing company .

Table 1-1 slide 6 read it .

**Thank you …**

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