Drug Discovery and Development:

Research starts with a hypothesis (idea), in that step the drug is discovered - the chemical substance- and the number one step is to test the efficacy, whether the drug produces an effect or not, without producing side effects, and the most serious side effect is death. For example, if you give a drug that produces an effect but kills 50% or 60% of the animals then it’s not a useful drug, and because we have so many other studies and very expensive ones, the efficacy is tested first.

What helps the idea we mentioned (hypothesis), is the experience of different people in the area, isolation of humeral substances in your body that have some biological activities and identification of their chemical structure. Now, once we’ve identified them in the body we are able to synthesize such drugs.

In addition, advanced technology helps even with complex proteins or glycoproteins. We use a method by which we can manufacture such proteins recombinantly in human technology or genetic engineering, etc.

Also, we discovered that it’s not necessary to synthesize the whole protein, as the active part of the protein produces the effect. For example if we have a 40 amino acid polypeptide while the drug that’s used for the same purpose is composed of only 15-20 amino acids, as the only active part has been used, and this helps in the availability of required materials for different synthetic procedure.

Now, testing the efficacy is carried out either in vitro or in vivo.

*In vitro*:

The organ is isolated from animals, such as bronchi, intestines, heart, etc. and it is placed in an organ bath and then the drug is injected in the organ or the bath (water that’s surrounding it) the response will be recorded by an electrode and physiological reporter, for example dilation or constriction of the bronchi, or even an increase or decrease in heart rate.

- an agonist has the same effect of the drug, while an antagonist has an opposite effect, and they are used in such experiments. So, if the antagonist is given followed by the agonist then there will be no effect as the effect by the agonist has been reversed by the antagonist.

*In vivo (animal models)*:

The animal models either have the disease or you interfere and cause them to have the disease, for example some rats have hypertension or diabetes, or the disease can be induced by utilizing the available information about the pathophysiology of that certain disease (knowing the defect behind it). So for an animal with hypertension, for example, I can test all antihypertensive drugs (drugs that will lower blood pressure) which act by different mechanisms and test the efficacy.

so supposing the drug so far is excellent, produces a good effect without producing a side effect – it doesn’t kill so much animals-, now the pharmacokinetic parameters have to be determined as well as the mechanism of action of the drug (pharmacodynamics), determination of this is not that difficult and I can extrapolate the data to human beings.
Note that all the previous tests were conducted in the preclinical stage, before the clinical stage, which involves using human beings. However, before reaching that stage we have to make sure that drug is safe and effective.

So far,

- The efficacy has been tested in the animal model (in vivo) and in vitro.
- The effective dose has been determined.

Safety is tested by conducting toxicity studies, which are carried out by giving increasing and large doses (remember that we have already determined the effective dose) to animals of course, as it’s illegal to be conducted on humans. Two parameters are used to assess the safety in human beings,

- LD$_{50}$ (the median lethal dose), which is the dose that results in the death of 50% of the animals tested.
- ED$_{50}$, which is the dose that produces an effect in 50% of the animals tested.

Now, let’s suppose the LD$_{50}$ was 10 milligrams for a 1kg rat, so by taking 60 kg as an average mass for a human being, the LD$_{50}$ would be $60 \times 10 = 600$ milligrams.

The further the LD$_{50}$ is from the ED$_{50}$ the better (safer), the more therapeutic the drug is, and this will be discussed later on, Godwilling.

Those studies are acute toxicity studies, which test the acute effect of large doses of the drug.

The following step is to assess chronic toxicity by using multiple doses. The first dose is given over a long period of time, during which animals are observed: their weight, intake, urine output, everything. After that the animals are killed, all organs are taken to be examined histopathologically to see whether there is any toxic effect on any organ.

If long toxicity excellent.11:28 If LD$_{50}$ is far away from the dose which produces an effect then it’s an excellent drug but remember that the safety and efficacy have already determined previously.

There are other tests that must be done before marketing the drug:

Mutagenicity, Genotoxicity, Teratogenicity: I have to prove before reaching the clinical stage whether or not the drug produces congenital malformations (تشوهات خلقية) in fetuses, this can be performed either in vitro or in vivo. No drug agency FDA, for example, will accept the drug or approve it to be used on humans before this test. That’s why for example we hear that certain drugs shouldn’t be given to a pregnant lady (contraindicated to be given to pregnant lady).

In vivo: the drug is injected to a pregnant animal, rat for example, then the animal is killed and the fetuses are examined.

Note: rats are a very good model for pregnancy as they have a 20-days pregnancy duration, give birth to 8-16 fetuses, they get pregnant immediately, their hormones are really similar to those of humans.
especially those controlling the menstrual cycle, although they don't bleed, but their menstrual cycle hormones are the same as humans.

Thalidomide, for example, is an analgesic that was used for headache, which is common in pregnancy as well as nausea and vomiting, so when pregnant women took this drug, it induced congenital malformations such as lost fingers and lost arms, Spina Bifida**, Micro Encephaly**.

It must be noted that some drugs, especially those used in the management of cancer are approved by drug agencies even if it is teratogenic, and they are available in drugstores, the solution is just not to give this drug to pregnant ladies.

Supposing there is a pregnant lady suffering from a disease and there is no alternative but to give her a teratogenic drug (exaggerated example), should you take the risk? Yes, because if the lady dies, the baby will die as well. So the drug is given and then the baby is monitored for any congenital malformations detected by amniocentesis** or Ultrasound, etc. if a malformation was detected abortion is done, but the lady’s life was saved.

Now, yet another test is to be done: carcinogenic studies, although they’re not necessary to be performed before marketing, the drug can be approved without such studies, as the detection of carcinogenicity takes a long time, but it should be done eventually, whether or not the drug will produce cancer.

There are some hints if the drug is carcinogenic:

- If the drug contains highly reactive roots, with a very toxic chemical structure. And this were chemists are important.
- If the drug is mutagenic, it has high (potential)incidence for it to be carcinogenic, and so carcinogenic studies should be performed but as mentioned earlier not necessarily before using it on human beings.

Now, we’ve finished efficacy, toxicity assessment, and a bit of kinetics, now we move to human beings.

There are 4 major phases of what is known the Clinical Drug Trials, which should be performed before marketing the drug.

A new subphase was added in 2006, Phase 0, it’s a very quick phase performed on a small number (10-15) of healthy individuals just to assess the pharmacokinetics and pharmacodynamics, to give us an idea about whether or not the kinetics in the human will behave exactly the same as in animals(remember the extrapolation of data from animals to humans) and whether the drug is promising to proceed with further studies or not.

It’s stirring controversy, though, as a number of countries disagree of performing this phase, claiming it’s not necessary because it has nothing to do with the assessment of the efficacy or safety, due to the fact that a sub therapeutic dose is being used (small doses or micro-dosing).
Phase I

- The first phase where the drug is used for the first time.
- It establishes the dose level at which signs of toxicity first appear.
- 20-80 healthy men/women at ages 18-45
- Under this phase bioavailability-bioequivalence studies are conducted, will be discussed later on with the discussion of kinetics, Godwilling.

The dose that we believe to be therapeutic is used, and then we assess whether or not there are any side effects, you may withdraw some blood from a volunteer in order to assess the kinetics and the dynamics.

If the dose given gives no sign of side effect, then it’s increased till a side effect appears. So, safety is being assessed here, as we’re exceeding even the therapeutic dose to see just when does it cause a side effect.

The ethics of this phase are controversial, as the volunteer is given increasing doses until a side effect appears, e.g. nausea or vomiting, but it never reaches death as LD_{50} has been determined on animals and so we use a dose that’s far away from it.

However, it’s a phase that must be done, and it’s conducted in the hospital with all needed equipments so that if he/she suffers from nausea/vomiting an antiemetic (a drug that is effective against vomiting and nausea) would be supplied, or from bronchoconstriction then bronchodilators would be available, or if there is fear of sever anaphylaxis a respirator would be supplied as well, so it’s conducted carefully.

So far,

- Efficacy, safety, toxicity studies and phase 0 have been passed.
- A suitable dosage has been determined.
- Phase 1 has been passed successfully,

now we use the drugs in patients.

Phase II

Involves administration of drugs to patients, it’s mandatory (إجباري) that such patients have only one problem (one disease), and this establishes the optimal range of the effective dose. And this is important for establishing what is known as dose response curves studies which are essential and related to the dynamics of the drug.

- 80-100 patients, with one problem
- Assesses the safety of the drug and at the same time I can withdraw a blood sample to assess the kinetics in such a way. Patient may behave differently as compared to normal healthy individuals, and so a larger number of patients is required and that’s why phase III is done.
Phase III

- The same as phase II with the difference that the number of patients increases up to 250-1000, regardless to the population number.
- Assesses safety and efficacy
- Could detect effects/side effects not observed in the previous phase.

Phase IV (Post marketing studies)

Once the drug is available in the market we ask all people in the medical area (professionals) to observe their patients for the side effects, new side effects, or new uses. Examples: aspirin and Viagra –in the prev. lect.-. In addition, carcinogenicity may be detected by these studies.

As a result from these studies many drugs have been removed from the market after years of use, for many reasons,

a. appearance of severe side effect,
b. large number of death numbers reported for the long use of such drug,
c. Carcinogenicity potential.

Placebo control

Placebo is a drug or a tablet containing all the ingredients of the drug except the active ingredient, for example Paracetamol is an active ingredient in a certain drug (Panadol, Tylenol) so the placebo would contain all ingredients but Paracetamol, and then a comparison is made to study the effect with and without placebo.

At some cases patients taking the placebo became better than those taking the real drug, and that’s due to psychological reasons. An example was given from the dr himself, as he used to take 2 pills of revanin whenever he had a headache, a year ago he started taking only one and it’s working with him.

Sometimes this is considered not ethical, because some of the patients are taking the new drug, while the others aren’t taking any, but it’s controlled meaning that patients are observed well by physicians, all these tests should be conducted in hospitals. – couldn’t quite get what the dr. said 26:28-

Ethics

Before doing a test on any volunteer whether on healthy individuals in phase 1 or on patients in phase 2 and 3, his/her agreement must be taken and discuss the whole thing with them, awaring them of what they’re most probably going to face and so on.

Before that you’re (sorry couldn’t make sense of what the dr. said 28:44, but in the slide it’s “full detailed protocol”) should be approved by the ethical committee, the institutional review board (IRB).
Volunteers should sign an informed consent (approval) form, and should be insured for life and damage.

Notes:

- Previously, money was given for volunteers but not anymore.
- Remember that the dose used in these phases (2,3) is much lower than that was used in phase one that lead the first appearance of a side effect, so these phases are safer than the first ones.

Branches of pharmacology (pharmacokinetics) usually answer these questions:

- How much of a drug to give (dose)?
- How frequent a drug should be given? Related to biological half life ($t_{1/2}$)
- When to give it? Before or after meals-whether or not there is an effect of food, at bed time, PRN**, etc.
- How to give it? Administration.

**Administration Routes:** the way the drug is taken, either Systemic, enters the systemic circulation or Local (topical). Notice that a good drug is available in many dosage forms, so as to suit different patients

**Systemic routes:**

- Oral: the most convenient way, there are many forms of administrations, such as tablets, capsules, suspensions or syrups. Note that all studies have been conducted supposing that these forms are taken with 200ml of water, except for syrups of course.
  There are different delivery systems: IR immediate release, very quickly absorbed and SR sustained release system, slowly absorbed to systemic circulation.
  **Suspensions: a powder and water added to it, usually used for children. Must shake it well before use every time.

If a patient is suffering from nausea or vomiting, he can’t take it orally, or if the absorption of the drug to systemic circulation would cause him problems, he can be given rectal suppositories instead of orally and so on.

- Parenteral route: injectable dosage form
  1. Subcutaneous S.C
  2. Intramuscular I.M, there is a depo-injectable route, deep in the muscle and the drug acts for a very long duration, for atleast 3-6 months.
  3. Intravenous I.V

- Transdermal implants or Sub dermal implants that can act for at least 5 years.
• Intrathecal or intraspinal, for drugs that are intended to reach the CNS so this way they reach the CSF and eventually the brain. However, if it’s taken orally or intravenously then it won’t be able to cross the blood brain barrier and so it won’t reach its destination.
• Buccal (tab), sublingual (tab) - kept in the mouth under the tongue -, rectal (suppositories)
• Inhalation(sprays)

There has been a great improvement in dosage forms and routes of administration. For example if a person suffers from severe pain in a certain joint, the drug may be injected *intra-articularly* (inside the joint).

**Topical (local administration)**

Ointments and creams and skin patches can be acting locally. -check the slides-

There’s a misconception that applying a drug to skin is very safe (that it’s purely local), but it’s not. The drug may be lipid soluble and so will be absorbed to systemic circulation. For example, Cushing syndrome (resulting from excess cortisol in blood) has been reported following locally applied steroid of cortisone, so you must bear in mind that 1% of the applied dose will be absorbed.

The major cause of Cushing syndrome is drug induced (steroids are likely used in medicine), not the adenoma** in the adrenal gland.

**Factors affecting the dose**

- Age, children require lower doses.
- Weight, calculation of the dose per kg is the best, obese individuals require higher doses than normal ones.
- Route of administration, oral route requires higher dose as compared to parenteral dose, related to bioavailability.
- Gender, females require lower dosages.

**Factors affecting the administration**

- Physicochemical properties, e.g. if the drug is broken down by the stomach acidity, then it shouldn’t be given orally.
- Site of action, CNS example mentioned earlier.
- Status of the patient, if the patient has nausea and vomiting, the drug shouldn’t be given orally, it’s given paranterally.
Dosage interval, if the drug must be given every hour, it’s not convenient to give this drug intravenously, not even subcutaneous is convenient eventhough it’s possible, so it’s given in another form.

Drug sources:

- Natural:

Plants: atropine and digoxin. Animals: bovine-insulin, porcine-insulin (insulin taken from cows and pigs) it’s available, but are provided upon request, it’s cheaper than human insulin.

Drug companies go over killed cows worldwide and ask for whatever is not needed, for example they take natural Thyroid and thyroxin. Natural human thyroxin is used as well, and there are available tablets of it, and it’s used in the management of hypothyroidism.

- Semisynthetic:

The Insulin that is taken from pigs differs in one amino acid, as the insulin structure is composed of a polypeptide with two chains, Chain A and Chain B, and disulfide bonds between them.

The difference between porcine insulin and human insulin is in the amino acid, so there is no such great difference. So, it could be used in human beings. Allergy is more frequent with pure form as there must be some contamination from the animal debris or the precursor of insulin.

So what they did to improve the situation of animal insulin, was to change the animal’s different amino acid with the human amino acid. If the animal’s is alanine and the human’s is serine then alanine is removed and replaced with serine, and so it becomes human insulin.

- Synthetic:

Once we knew the structure of human insulin, it became easily synthesized using recombinant Technology. This source also allows us to synthesize(manufacture) different agonists and antagonists.

Growth Hormone

The pituitary used to be taken after immediately after a person dies without even the agreement of the parents, unlike the cornea which requires an approval, due to the fact that there is no bleeding and the procedure is simple, as a probe is inserted intranasally, the pituitary is taken out, and then the Growth hormone is extracted, to be used in cases of Growth hormone deficiency and dwarfism. it was highly effective and the major source, with no other source.

Unlike insulin, bovine or porcine growth hormones can’t be used for human, because the structure is completely different. Actually it can cause Creutzfeldt–Jakob disease CJD that leads to death.
Drug Nomenclature

I. The drug has chemical name (not used in pharmacology).

II. Generic name that is most commonly used in pharmacology, it is assigned by the manufacturer or inventor, a non-proprietary name.

   Some books call it official name but it’s preferable to differentiate the official form generic name. The difference between them is that after the drug is discovered the official name is followed by BP or USP [approved by the British pharmacopeia or US pharmacopeia].

III. The trade name: the name used by practitioners or physicians to prescribe and dispense drugs by the pharmacists.

   for example, acetylsalicylic acid is the chemical name while the generic name is aspirin.

Pharmacokinetics:

mathematical representations of the process; absorption, distribution, metabolism and excretion.

Absorption: the passage of the drug from the site of administration to the systemic circulation, in order for it to reach its site of action.

Remember that in drug discovery studies, pharmacokinetics were assessed. So this is the first parameter (calculation) of those mentioned earlier.

Behavior of drugs in plasma:

- Bioavailability: the fraction(percentage) of the given dose that gets into the blood. For example if 100 mg of a certain drug is given, and then you measure the drug in your blood you find it’s 70mg so 30 mg is lost in the intestines if it’s administrated orally, and so the bioavailability is 70%. However, if it were administrated intravenously the bioavailability would be 100% and that’s why it requires lower doses, lost fraction in the GI tract was bypassed.

Suppose that you have a 100mg drug with the bioavailability of 5%, 5mg will be absorbed, 95mg will be lost in the intestines, so we can generalize *that drugs with low bioavailability are ineffective orally, with exceptions, of course.*

However, you manage to find some drugs with a 5% or 10% bioavailability and they’re out there being sold as tablets and capsules and are used orally, that’s because that’s exactly what we want 5%, the rest of it doesn’t cause side effects, and it passes all requirements and it gives an effect, even though we’ve lost the rest of the drug (& paid extra money for something that’s going
to be lost). That’s why chemical modifications are done to the drug in order to have another drug with better bioavailability.

- Protein binding: when the drug enters the blood it binds to plasma albumin or globulin.
  1. This binding represents a reservoir to the drug. In blood there’s a bound form, and a free form that can pass through membranes and will reach the site of action so it’s the active form. There’s an extent of binding Extensively bound drugs to plasma proteins usually have longer duration of action in comparison with drugs with less binding capacity.
  2. It represents a mean by which the drug travels in the blood.
  3. It’s a site of drug-drug interactions. Suppose a drug was given, with all the studies previously carried out assuming only 10% of that drug will be in its free form, and then another drug is given and it interferes with the previous drug and competes with it on the binding site of plasma protein, leading to an increase the free form percentage, and this affects the toxicity. So, to suit the studies, only 10% from the bound form should be freed, does the action, gets excreted and then another 10% of the bound form converts to the free form and the cycle goes on again and again till it’s over.
  
** remember that when we say that 70% of the drug is in the blood, with 50% protein binding, then the bioavailability -not the dose- is 70%.

Notes:

** recombinant : adjective  Referring to a structural rearrangement or 'shuffling' of genetic material that –in this case– Is deliberately generated under controlled experimental conditions, as in recombinant DNA (online medical dictionary)

**microencephaly Etymology: Gk, micros: small, egkephalos: brain. The condition of being born with an abnormally small brain.

** wikipedia : Spina bifida (Latin: "split spine") is a developmental congenital disorder caused by the incomplete closing of the embryonic neural tube. Some vertebrae overlying the spinal cord are not fully formed and remain unfused and open

** wiki: Amniocentesis (also referred to as amniotic fluid test or AFT) is a medical procedure used in prenatal diagnosis of chromosomal abnormalities and fetal infections.

In the exam you must watch out for the terminology of the question, for example if the questions is “what is the major reported side effect to insulin therapy” is different from “side effects reported from using insulin” in the first case you choose just one, but in the second case you choose all of the above.

**wiki answers :"PRN" stands for Pro Re Nata, which is Latin literally meaning "For the thing born." In medicine, it means "As needed" or "As the situation arises". Usually followed by something along the
lines as "Not to exceed 30 mg in 24 hours."

** wiki: An adenoma is a benign tumor (-oma) of glandular origin.

“Without education, you’re not going anywhere in this world.”
~malcolm X (alhajj malik shabbaz)

Mira Younis