Steps in Drug Development

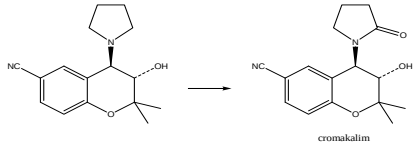
- Target selection and validation
- Assay development
- Acquisition of compounds
- Screening and data analysis
- Lead optimization
- Preclinical evaluation
- Clinical trials

Pharmacology

- Pharmacological testing determines effects of the candidate drug on the body. Toxicology studies are conducted to identify potential risks to humans.

Problems to Consider

- Pharmacokinetics
- Metabolism
- Prodrugs



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- Synthesis/Manufacturing process

Metabolism of Drugs

There are two important aspects in drug design and drug strategies to improve :

- **Pharmacodynamics properties**: to optimize the interaction of the drug with its target.
- **Pharmacokinetics properties**: to improve the drug's ability to reach its target & to have acceptable lifetime.

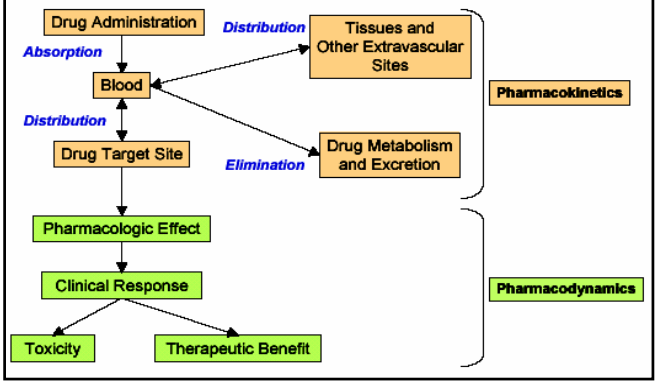
- Pharmacodynamics and pharmacokinetics should have equal priority in influencing which strategies are used and which analogues are synthesized.

Pharmacology: Its Scope

- **Pharmacokinetics:** study of the absorption, distribution, metabolism and excretion of drugs.

- **Pharmacodynamics**: study of the molecular, biochemical, and physiology effects of drugs on cellular systems and their mechanisms of action.

Pharmacokinetics and Pharmacodynamics



Metabolism of Drugs

- The body regards drugs as foreign substances, not produced naturally.
- Sometimes such substances are referred to as “xenobiotics”
- Body has “goal” of removing such xenobiotics from system by excretion in the urine
- The kidney is set up to allow polar substances to escape in the urine, so the body tries to chemically transform the drugs into more polar structures.

Making drug less resistance to Metabolism

- Drug that is extremely stable to metabolism and is very slowly excreted can cause problems as that is susceptible to metabolism. Such as cause toxicity and side effects.
- Therefore, designing drugs with decreased chemical and metabolic stablility can sometimes be useful.

Prodrugs

- Prodrugs are compounds which are inactive in vitro and converted in the body to active drug.
- *They have been useful in talking problems such as:*

1. Acid sensitivity
2. Poor membrane permeability
3. Drug toxicity & side effects
4. Bad taste
5. Short duration of action
6. Solubility
7. Stability

Prodrugs

A prodrug is drug which is given (taken) in an inactive form. Once administered, the prodrug is metabolized by the body into the biologically active compound.

- Prodrug strategies are used to overcome a variety of problems by:
- **Altering solubility**
  - Making a compound either more or less soluble may assist in achieving the desired formulation
- **Improving membrane permeability**
  - Absorption into a cell means crossing a hydrophobic cell membrane. If a drug is too polar drugs it may not pass the membrane, but too non-polar and it may not come back out!
- **Slow release of the active agent**
  - If a drug is eliminated from the body quickly then an effective dosage cannot be sustained. Slow release of the active agent by controlled release from a prodrug allows a more controlled dosage of the active being released into the body.
- **Masking drug toxicity or side effects**
  - Many anticancer agents are cytotoxic, but it is the cancerous cells only which we want to kill. Masking toxicity can be achieved by prodrugging and the active agent is accumulates preferentially in the tumour (due to leaky vasculature).

Prodrugs

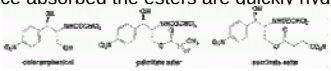
- A metabolic enzyme is usually involved in converting the prodrugs to the active forms.
- Good knowledge of drug metabolism and enzymes allows the medicinal chemist to design a suitable prodrug.
- Not all prodrugs are activated by metabolic enzymes.
  - *E.g. photodynamic therapy involves the use of an external light source to activate prodrugs.*
- When designing a prodrugs, it is important to ensure that the prodrug is effectively converted to the active drug once it has been absorbed in blood supply.
- It is also important to ensure that any groups that are cleaved from the molecule are non-toxic.

Prodrugs

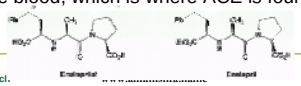
- Prodrugs are inactive compounds which are converted to active drugs in the body-usually by drug metabolism.
- Esters are commonly used as prodrugs to make a drug less polar, allowing, it to cross cell membranes more easily. The nature of the ester can be altered to vary the rate of hydrolysis.
- Introducing a metabolically susceptible N-methyl group can sometimes be advantageous in reducing polarity.
- Prodrugs with a similarity to important biosynthesis building blocks may be capable of cross cell membranes with the aid of carrier proteins.

Prodrugs - examples

- The antibiotic chloramphenicol is very bitter, but the palmitate ester does not get absorbed by the tongue so much when taken orally and so is more palatable. The succinate ester on the other hand makes it more soluble making intravenous formulation more effective. Once absorbed the esters are quickly hydrolysed.



- The ACE inhibitor enalaprilat is potent *in vitro*, but is poorly absorbed and so not very effective *in vivo*. The ethyl ester enalapril, however, is absorbed much better but is a weak ACE inhibitor. It is hydrolyzed to the carboxylic acid by esterase enzymes in the blood, which is where ACE is found.



Toxicology

- It is often found that a drug fails clinical trials because of its toxic side effects.
- This may be due to toxic metabolites, in which case the drug should be made more resistant to metabolism as described previously.

Reducing Toxicity

- Strategies designed to target drugs to particular cells or tissues are likely to lead to safer drugs with fewer side effects.
- Drugs can be linked to amino acids or nucleic acid bases to target them against fast-growing and rapidly divided cells.
- Drugs can be targeted to the GIT by making them ionized or highly polar such that they can not cross the gut wall.

Reducing Toxicity

- The CNS side effects of peripherally acting drugs can be eliminated by making the drugs more polar so that they do not cross the blood-brain barrier.
- Drugs with toxic side effects can sometimes be made less toxic by varying the nature or position of substituents, or by preventing their metabolism to a toxic metabolite.

Pharmacology and Toxicology

- Toxicity tests are carried out in vivo on drug candidates to assess acute and chronic toxicity. During animal studies, blood and urine samples are taken for analysis.
- Individual organ are analyzed for tissue damage or abnormalities.
- Toxicity testing is important in defining what the initial dose level should be for phase I clinical trials.
- Drug metabolism studies are carried out on animals and human to identify drug metabolites. The drug candidate is labeled with an isotope in order to aid the detection of metabolites.
- Pharmacology testes are carried out to determine a drug's mechanism of action and to determine whether it acts at targets other than the intended one.
- Formulation studies aim to develop a preparation of the drug which can be administered during clinical trials and beyond.
- The drug must remain stable in the preparation under variety of environmental conditions.

Preclinical Toxicology Testing

- Preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product.
- This testing is critical to a drug's eventual success and, as such, is scrutinized by many regulatory entities.
- During the preclinical stage of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared.
- Studies taking place during the preclinical stage should be designed to support the clinical studies that will follow.

Preclinical Toxicology Testing

- Acute Studies
- Repeated Dose Studies
- Reproductive Toxicity Studies
- Carcinogenicity Studies
- Toxicokinetic Studies

Formulation Development

- Preformulation
- API characterization
- Formulation development and optimization
- Container/closure characterization and selection
- Method development and validation
- Process development and scale-up support
- Stability studies
- Product complaint analysis and testing

Formulation

Delivery, Packaging Development

- Drug developers must devise a formulation that ensures the proper drug delivery parameters.
- It is critical to begin looking ahead to clinical trials at this phase of the drug development process.
- Drug formulation and delivery may be refined continuously until, and even after, the drug's final approval.
- Scientists determine the drug's stability—in the formulation itself, and for all the parameters involved with storage and shipment, such as heat, light, and time.
- The formulation must remain potent and sterile; and it must also remain safe (nontoxic).

Formulation Studies

- DRUG +

Additive: filler, lubricant, coating, stabiliser, colour, binder, disintegrator

Dosage form: capsule, tablet, injection, other?

Manipulate duration/profile: e.g. sustained release

Bioequivalence

Bioavailability

Ease of use

Bioanalytical Testing

- Bioanalytical laboratory work supports most of the other activities in the drug development process.
- The bioanalytical work is key to
  - Proper characterization of the molecule,
  - Assay development,
  - Developing optimal methods for cell culture or fermentation,
  - Determining process yields, and
  - Providing quality assurance and quality control for the entire development process.
- It is also critical for supporting preclinical toxicology/pharmacology testing and clinical trials.

Drug Development

Three main issues are involved in drug development

1. The drug has to be tested to ensure that it is not only safe and effective, but can be administered in a suitable fashion. This involves preclinical and clinical trials covering toxicity, drug metabolism, stability, formulation, and pharmacological tests.
2. There are the various patenting and legal issues.
3. The drug has to be synthesized in ever-increasing quantities for testing and eventual manufacture (this is known as chemical and process development).

Drug development phases

- Clinical trials are designed to:
  - Determine safety and tolerance in man
  - Pharmacokinetics
  - Bioavailability for a range of doses
  - Determine the pharmacological profile

Clinical Trials

Involves four phases

- In phase I healthy volunteers are normally used to evaluate the drug's safety, its pharmacokinetics, and the dose levels that can safely be administered.
- Phase II studies are carried out on patients to assess whether the drug is effective, to give further information on the most effective dosing regime and to identify side effects.
- Phase III studies are carried out on larger numbers of patients to ensure that results are statistically sound, and to detect less common side effects.
- Phase IV studies are ongoing and monitor the long-term use of the drug in specific patients, as well as the occurrence rare side effects.

Stages in clinical Studies

Phase 1
- Small number of healthy volunteers or patients
  - Toxicity & tolerated dose range, PK/PD studies

Phase 2
- Several hundred patients with specific disease
  - Therapeutic effectiveness (dose/conc/response)
  - Short term safety, dosage strategy for Phase 3

Phase 3
- Several thousand patients
  - Clinical safety & efficacy (overall risk/benefit)
  - Further refine dose/conc/response
  - Qualitative & quantitative assessment of ADRs

Phase 4
- Post-marketing surveillance & ADR reporting

Clinical Trials

- Patent are taken out as soon as a useful drug has been identified. They cover a structural class of compounds rather than a single structure.
- A significant period of the patent is lost as a result of the time taken to get a drug to the market place.
- Patents can cover structures, their medicinal uses, and their method of synthesis.
- Regulatory bodies are responsible for approving the start of clinical trials and the licensing of new drugs for the market place.

Clinical Trials

- Drugs that show promise in a field which devoid of a current therapy may be fast tracked.
- Special incentives are given to companies to develop orphan drug-drug that are effective in rare diseases.
- Pharmaceutical companies are required to abide by professional codes of practice known as good laboratory practice, good manufacturing practice, and good clinical practice.
- Chemical development involves the development of a synthetic route which is suitable for large scale synthesis of a drug.

Clinical Trials

- The priorities in chemical development are to develop a synthetic route which is straightforward, safe, cheap, and efficient, has the minimum number of synthetic steps, and provide a consistency good yield of high-quality product that meets predetermined purity specifications.
- An early priority in chemical development is to define the purity specifications of the drug and to devise a purification procedure which will satisfy these requirements.
- Process development aims to develop a production process which is safe, efficient, economic, environmentally friendly, and produces product of a consistent yield and quality to satisfy purity specification.
- Drugs derived from natural sources are usually produced by harvesting the natural source or through semi-synthetic methods.