
# *Clinical pharmacology*

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# Sequence..

1. Introduction
2. Pharmacokinetics
3. Pharmacodynamics
4. Factors affecting therapeutic outcome
5. Drug development and licensing procedures

# Introduction..

- Clinical pharmacology deals with the actions,mechanisims of actions,uses,adverse effects and fate of drugs in humans and to underpins all aspects of drug therapy from novel drug development through to safe, effective prescribing

# Types of drugs..

- Two types of drugs
- SMALL- MOLECULE DRUGS

  Small organic molecules(<500kDa)
- LARGE-MOLECULES DRUGS

  large organic molecules(>500kDa)

# Cont..

- Biological therapy ,biotherapeutics and biological medicinal products are all terms used interchangeably and can be used to describe therapeutic agents that are produced by or extracted from a biological source
- These include
- Recombinant proteins
- Monoclonal antibodies
- Fusion proteins and blood products
- Immunological medicinal products such as sera and vaccines
- Allergens and advanced technology products such as gene and cell therapy products

# Common terms used in clinical pharmacology

| Term | Definition |
| --- | --- |
| Drug disposition | The absorption, distribution, metabolism and elimination of a drug |
| Bioavailability | The fraction of a drug absorbed into the systemic circulation |
| Volume of distribution | A measure of the *apparent* space in the body available to contain a drug calculated according to the amount of drug given, and the concentration found in the systemic circulation |
| Clearance | A measure of the body's efficiency in eliminating a drug from the systemic circulation |
| Elimination half-life | A measure of the rate of removal of a drug from the systemic circulation |

# Cont..

| | |
|---|---|
| Equilibrium dissociation constant ($K_D$) | A measure of drug/receptor binding affinity (a drug with high affinity binding will have a low $K_D$) |
| Half maximally effective concentration ($EC_{50}$) | A measure of drug potency |
| Median effective dose ($MD_{50}$) | Dose of drug required to produce a specified effect in 50% of the population |
| Lethal effective dose ($LD_{50}$) | Dose of drug required to cause death in 50% of experimental animals (pre-clinical) |
| Therapeutic window | Range of steady state drug concentration required to produce the desired clinical effect with minimal toxicity |

# Pharmacokinetics..

- Describes the processes involved in drug absorption, distribution, metabolism and elimination i.e what the body does to the drug
- **ABSORPTION**

Describes the movement of a drug from its site of administration to the central compartment(usually blood or plasma)

- **ROUTES OF ADMINISTRATION**
- Topical
- Oral
- Parenteral

# Cont..

- **TOPICAL**

  **in a ski**n disease ,a topical approach to treatment is often preferred as it allows direct application of the drug to the diseased area

- Not all drugs can be effectively delivered in a topical form
- The decision of topical or systemic approach depends on the nature, extent, site and severity of disease, practicability and patient choice
- A combination of topical and systemic approach can also be used to minimize the side effects or toxicity

# Cont..

- **ORAL**

  oral dug administration is convenient for patients but bioavailability is highly variable and dependent on drug characteristics ( e.g. Lipophilicity, pH), concomitant food intake (e.g. Chelation of tetracyclines by calcium in milk) and rate of gastric emptying

- Drug formulation is also important like enteric coated preparations are useful for drugs which causes gastric irritation such as prednisolone

# Cont..

- **PARENTERAL ADMINISTRAION**
- It includes intravenous, intramuscular and subcutaneous
- Circumvents the gastrointestinal tract with consequent improved drug bioavailability
- Therapeutic proteins have limited oral bioavailability due to intestinal enzymes and poor permeability across the intestinal mucosal membrane barrier
- Following S/C administration, a drug is absorbed via lymphatics and/or capillary networks into systemic circulation

# Cont..

- **FACTORS AFFECTING DRUGS ABSORPTION AND BIOAVAILABILITY FOLLOWING S/C ROUTE**
- Patients characteristics( body, sex, age and activity level)
- Local factors at the injection site(e.g. S/C blood flow, adiposity)
- Injection technique, as well as drug specific factors( e.g. Formulation, volume, dose, concentration, presence of an Fc receptor and degree of glycosylation)

# Cont..

- **DISTRIBUTION**
- The volume of drugs distribution is mainly determined by its physiochemical properties( (such as charge and Lipophilicity, protein binding capacity and degree of active transport mechanisms
- Small molecule drugs are distributed into interstitial and intracellular fluids with well-perfused organs such as liver, kidneys and brain receiving most of the drugs initially and skin and fat levels accumulating more slowly
- Preferential accumulation of drugs in certain tissues may also be of clinical relevance e.g. accumulation of retinoid in adipose tissue needs dosing alteration in obese patient

# Cont..

- **METABOLISM**
- Occurs in two phases
- Phase 1 reactions are catalysed by cytochrome P450 (CYPs), Flavin-containing mono-oxygenases and epoxide hydrolases and leads to oxidation, reduction or hydrolysis of the drug
- Usually it results in loss of drug function, but for some drugs( so-called pro-drugs), it results in drugs activation(e.g. Mycophenolate mofetil is an ester pro-drug, which is hydrolysed to biologically active mycophenolic acid by plasma esterases)

# Cont..

- Phase 2 reactions catalyse conjugation of phase 1 products with second molecule( sulphate, glucoronic acid, glutathione, acetyl and methyl group)
- It inactivates potentially toxic phase 1 metabolites, and also facilitates drug elimination as a consequence of improved water solubility and increased molecular weight
- Drugs metabolizing enzymes are found in most tissues in body, including the skin, but are found in greatest quantity in GI tract ( liver, small and large intestine)

# Cont..

- **EXCRETION**
- Drugs are eliminated from the body either unchanged or as drug metabolites, with the kidney being the principle site of drug and drug metabolite elimination
- Renal function is therefore a critical factor in determining drug bioavailability and potential toxicity
- Therapeutic proteins are removed from the circulation and interstitial tissue fluids in a variety of ways including target mediated clearance, non specific endocytosis and formation of circulating immune complexes

# Pharmacodynamics..

- It is the study of the biochemical and physiological effects of drugs and their mechanisms of actions(i.e. What the drug does to the body)
- Most drugs work by interacting with a specific cellular macromolecules( drug target or drug receptor)
- This drug-receptor interaction ultimately alters tissue function and depends on
- The affinity and specificity of drugs /receptor binding
- The intrinsic activity of receptor-bound drug to activate the receptor
- **AGONIST..** the intrinsic activity of drug completely mimics the effect of endogenous ligand

# Cont..

- **ANTAGONIST..**Prevents or blocks this response
- **PARTIAL AGONIST..**partially activates or blocks the response
- **INVERSE AGONIST..**inhibits the activity by binding to and stabilizing the receptor in an inactive form
- **SYNTOPIC BINDING..**Drugs may bind to the same recognition site as the endogenous ligand
- **ALLOSTERIC OR ALLOTROPIC BINDING..**Drugs bind to different recognition site. This may b reversible or irreversible, competitive or non competitive

# Molecular mechanisms underlying drug actions

- Initially drug/receptor coupling may result in a direct effect on the cellular function, or convey a message to intermediary cellular signalling molecules(transducers)
- The receptor, its cellular target and any intermediary molecules are termed as ***RECEPTER-EFFECTOR SYSTEM or SIGNAL TRANSDUCTION PATHWAY***
- These transducer proteins mediate the actual physiological effect via generating, moving or degrading small molecules known as second messenger( NO or cAMP)
- This system allows cell to co-ordinate and to amplify, signals from multiple ligands
- This drug/receptor coupling with mechanism can be outside the cell, at the cell membrane or within the cell

# Extracellular mechanisms

- A number of drugs act outside the cell to affect cellular function, typically in one or two ways
- The first is to alter the activity of extracellular enzymes involved in the synthesis or degradation of endogenous signalling molecules( e.g. ACE #)
- Second is by directly interacting with the endogenous ligand to prevent binding to its site of action (e.g. Monoclonal antibodies such as TNF antagonists adalimumab or infliximab

**Table 14.2** Major mechanisms underlying drug actions.

| Structural family | Functional family | Physiological ligands | Effectors and transducers | Example drugs |
|---|---|---|---|---|
| *Transmembrane transduction mechanisms* | | | | |
| G-protein-coupled receptors | Muscarinic cholinergic receptors | ACh | $G_i$ and $G_q$; AC, ion channels, phospholipase | Botulinum toxin |
| | Eicosanoid receptors | Prostaglandins, leukotrienes, thromboxanes | $G_s$, $G_i$ and $G_q$ proteins | Montelukast |
| | Histamine receptors (1–4) | Histamine | $G_{q/11}$, $G_s$, $G_{i/10}$ | Fexofenadine, ranitidine |
| Ion channels | Ligand gated | ACh, GABA, 5-HT | Na+, $Ca^{2+}$, $K^+$, $Cl^-$ | Nicotine, gabapentin |
| | Voltage gated | None (activated by membrane polarization) | $Na^+$, Ca2+, $K^+$, other ions | Lignocaine |
| Transmembrane enzymes | Receptor tyrosine kinases | Insulin, PDGF, EGF, VEGF, growth factors | SH2 and phosphotyrosine-binding domain containing proteins | Herceptin, imatinib, vemurafenib |
| Transmembrane non-enzymes | Cytokine receptors | Interleukins and other cytokines | JAK/STAT, soluble tyrosine kinases | Janus kinase inhibitors |
| | Toll-like receptors | LPS, bacterial products | NF-κB, MyD88, IRAKs | Imiquamod |
| *Intracellular transduction mechanisms* | | | | |
| Nuclear receptors | Steroid receptors (includes retinoic acid receptors, retinoid X receptors) | Oestrogen, testosterone | Co-activators | Corticosteroids, alitretinoin, bexarotene |
| | PAR-ϒ | PAR-ϒ | | Thiazolidinediones, clofibrate |
| Intracellular enzymes | Cyclic phosphodiesterases | Cyclic GMP, cAMP | Protein kinase A, exchange proteins activated by cAMP, cAMP responsive element binding protein | Vasodilators, anti-inflammatory agents (apremilast, rofluminast) |

*Adapted from Blumenthal and Garrison 2011 [16].*

*ACh, acetyl choline; EGF, epidermal growth factor; GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine; IRAKs, interleukin-associated kinases; JAK, Janus kinase; LPS, lipopolysaccharide; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κB; PAR-ϒ, proteinase activated receptor ϒ; PDGF, platelet-derived growth factor; SH2, Src homology 2; STAT, signal transducers and activators of transcription; VEGF, vascular endothelial growth factor.*

# Drug toxicity and adverse effects..

- Drug toxicity can be divided into five categories based on the underlying mechanism
- **ON TARGET DRUG TOXICITY.** Modulation of primary, pharmacological target e.g. Receptor or enzyme leading to an exaggerated pharmacological response
- **OFF TARGET TOXICITY.** Interaction of a drug with targets other than the intended therapeutic targets e.g. H1 receptor antagonist terfenadine also inhibits cardiac potassium channel leads to fatal cardiac arrhythmias
- **BIOLOGICAL ACTIVATION OF DRUGS..** Toxic metabolites capable of binding to proteins DNA, and small molecules. E.g. Paracetamol induced hepatic necrosis is a classic example due to glutathione binding and depletion by the active intermediate metabolite N acetyl-p-benzoquineimine

# Cont..

- **ALLERGIC REACTIONS..**extends from type 1 to type 4 reactions, are not dose related and are generally unpredictable
- **IDIOSYNCRATIC DRUG REACTION..**very rare, significant adverse effects without any obvious underlying mechanism

# Cont..

**Table 14.3** Methods used to identify drug-related adverse effects and their respective roles within the lifetime of a drug, from drug development through to post-licensing pharmacoviligance.

| Method | Benefits | Problems |
|---|---|---|
| Clinical trials (phase I–IV) | Controlled<br>Rigorous collection of high-quality data<br>Will identify common, short-term side effects | Short term<br>Powered for efficacy not safety<br>Data may not be relevant to clinical practice<br>Will miss effects with long latency period |
| Spontaneous reporting | Identifies new/rare/unexpected adverse events and drug–drug interactions | May overestimate the risk (no denominator)<br>May miss common/less severe morbidity |
| Registries | Reflects real-life clinical practice<br>Population-based<br>May allow relative risk/benefit analysis<br>Allows collection of adverse effects with longer latency period | Incomplete datasets<br>Observational; multiple confounders<br>May lack control group |

# Factors that affect therapeutic outcomes..

- **DRUG CHOICE AND MEDICAL DECISION MAKING**
- Before initiating any therapeutic measures, a comprehensive assessment of the patient is essential, considering the disease that requires treatment in the context of the whole patient and shared treatment goals

# Clinical factors that affect drug pharmacokinetics and pharmacodynamics..

- **AGE..**
- Drug pharmacokinetics and pharmacodynamics are altered in very young and in very older people
- Growth and development during childhood is associated with marked physiological change, especially during infancy and puberty
- During infancy, stratum corneum is thinner and in childhood there is increased cutaneous perfusion and hydration as compared to adults
- Hepatic drug metabolizing enzymes are expressed at very low levels at birth and then undergo developmental changes
- With ageing, number of physiological changes occur including cutaneous atrophy, 40% reduction in hepatic blood flow with decrease activity of hepatic enzymes and decrease renal function which results in increase drug bioavailability and decrease drug metabolism and elimination

# Conception, pregnancy and lactation..

- Any drug exposure prior to, during or after conception can result in an adverse fetal outcome
- Drug exposure during embryonic weeks(2 to week 9) carries greatest risk of fetal malformation as this is when organogenesis occur e.g. Acitretin, isotretinoin and thalidomide are known for teratogenic effects during pregnancy
- Topical treatment is generally the safest route of drug during pregnancy
- In men, drugs may affect fertility and/ or spermatogenesis
- Some drugs like methotrexate, azathioprine, cytotoxic directly interacts with DNA and can cause congenital abnormalities

# Drug interactions..

- A drug's effect may be significantly altered by the co-administration of another drug with a consequent impact on efficacy and/or induction of toxicity
- The principle mechanisms underlying most drug interactions relate to drug-metabolizing enzymes and transporters
- For example, ciclosporin is extensively metabolized by CYP3A isoform. Co-therapy with erythromycin or litraconazole, both potent inhibitors of CYP3A, can lead to significant increase levels of ciclosporin, where as phenytoin, a potent inducer of CYP3A may reduce level of ciclosporin
- Drug transporter interactions arise either due to change in activity( increased or decreased ) or competition at a transporter level

# Patient adherence to treatment..

- **ADHERENCE..**patient follows the instructions they are given for a prescribed medication
- **NON-ADHERENCE..**patients donot follow the given instructions
- It is divided into
- Unintentional non-adherence
- Intentional non-adherence

# Cont..

***Causes of unintentional non-adherence***

- Poor comprehension or recall of the details of prescribed dugs
- Lack of access or ability to pay for treatment
- Difficulties applying or taking a medicine

**Causes of intentional non- adherence**

- When patient decides not to take the prescribed medicine
- Arises due to patients' beliefs
- Concerns or problems associated with their condition and/ or prescribed medicine

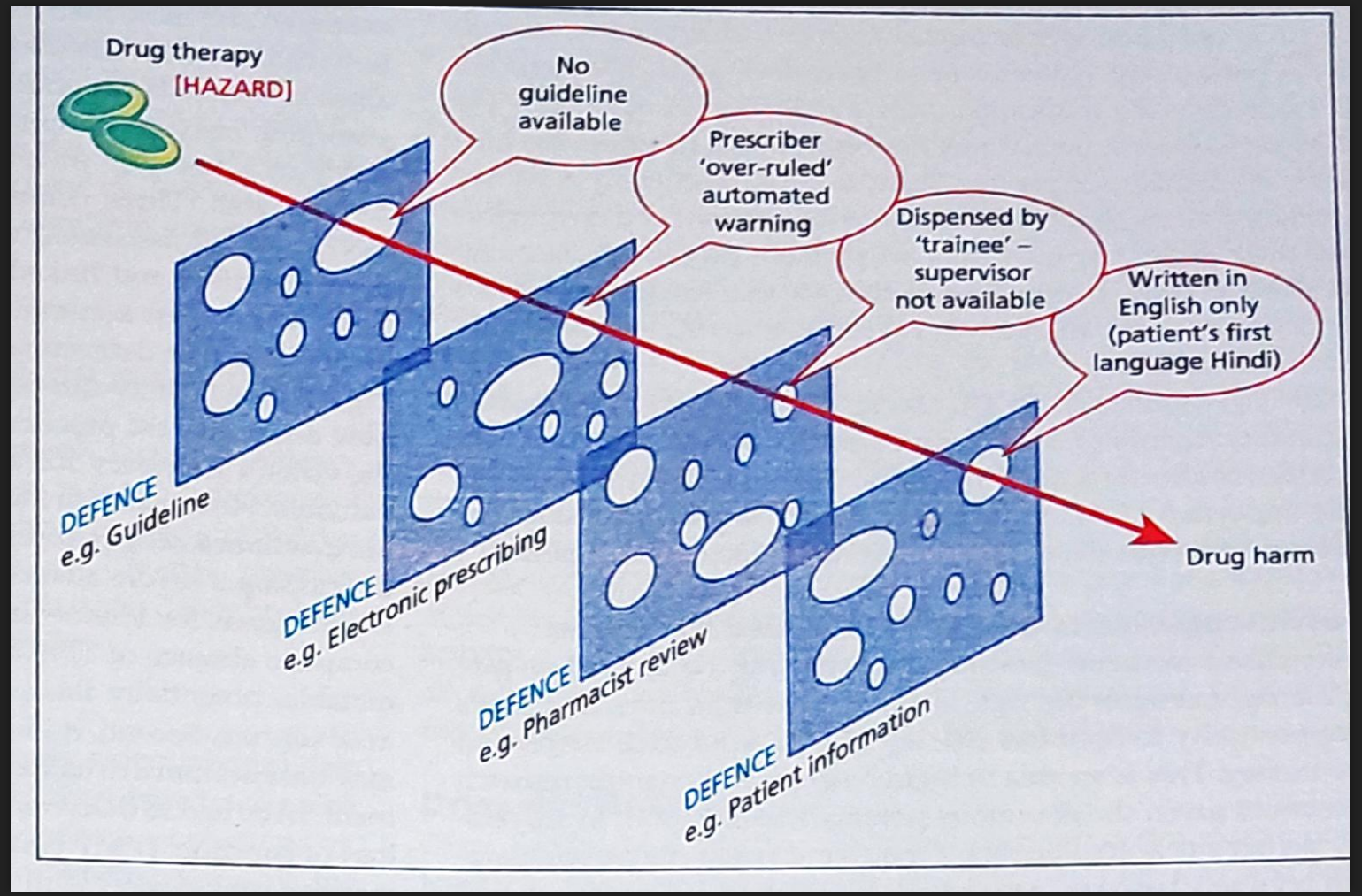
# Cont..

- **FACTORS THAT MAY IMPROVE ADHERENCE**

- Clear written and verbel communication
- Why and when treatment needs to be take
- Using the simplest dosing schedule possible
- Employing various techniques to remind and support patients

# Medicine errors

**Figure 14.2** Swiss cheese model to illustrate the cumulative effect of multiple failures (holes) in defence mechanisms that ultimately translate drug hazard into actual, drug-related patient harm. The 'holes' in the defence may be latent such as organizational flaws (e.g. no supervisor being present) or active (e.g. the prescriber actively overruling an automated alert). Understanding the origin of near misses and/or actual drug-related adverse events is a crucial step towards safer prescribing and the avoidance of preventable drug harm.



# Pharmacogenetics and personalized medicine

- **PERSONALIZED MEDICINE..**
- can be defined as giving the right drug to the right patient at the right time, and offers an opportunity to optimize efficacy, minimize adverse effects and save money
- **PHARMACOGENETICS..**
- Gene encoding drug-metabolizing enzymes, transporters and drug targets may all be subject to functionally relevant polymorphisms and are estimated to account for 15-30% of interindividual variation in drug response

# Cont..

- Much pharmacogenetics research has focused on genetic factors underlying differences in drug pharmacokinetics, and this has been largely driven by prior detailed knowledge about drug metabolic pathways
- Genetic variation in drug targets also play a major role in determining drug response
- Genes may also influence drug response through involvement in the underlying disease process

# Drug development and licensing procedures..

- The process of making drug that meets efficacy and safety requirements for use in patients is long, complex and extremely costly
- **Pre-clinical drug identification**
- The two principal approaches used to identify potential candidate medicines are
- **Phenotypic screening** investigates the effects or phenotypes, that a compound induces on cells, tissues or whole organisms and used to be the mainstay of new drug identification
- **Target-based screening.** This requires a detailed understanding of a molecular basis of a particular disease or pathogenic pathway

# Drug development..

- Once the candidate drug is identified , further optimization and testing is completed in a variety of in vitro, cell, organotypic and animal model


THANK YOU