Faculty of Pharmaceutical Sciences

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Dose response relationship, therapeutic index, combined effects of drugs and factors modifying drug action. Adverse drug reactions. Drug interactions (pharmacokinetic and pharmacodynamic) Drug discovery and clinical evaluation of new drugs -Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

DOSE-RESPONSE RELATIONSHIP

When a drug is administered systemically, the dose-response relationship has two components: dose-plasma concentration relationship and plasma concentration-response relationship. The former is determined by pharmacokinetic considerations and ordinarily, descriptions of doseresponse relationship refer to the latter, which can be more easily studied in vitro. Generally, the intensity of response increases with increase in dose (or more precisely concentration at the receptor) and the dose-response curve is a rectangular hyperbola. This is because drug-receptor interaction obeys law of mass action, accordingly.

E = E max * D/ KD +D

Where E is the observed effect at a dose [D] of the drug, Emax is the maximal response, KD is the dissociation constant of the drug-receptor complex, which is equal to the dose of the drug at which half maximal response is produced. If the dose is plotted on a logarithmic scale, the curve becomes sigmoid and a linear relationship between log of dose and the response is seen in the intermediate (30–70% response) zone, as can be predicted from This is not peculiar to drugs. In fact all stimuli are graded biologically by the fractional change in stimulus intensity, e.g. 1 kg and 2 kg weights held in two hands can be easily differentiated, but not 10 kg and 11 kg weights. Though the absolute difference in both cases remains 1kg, there is a 100% fractional change in the former case but only 10% change in the latter case. In other words, response is proportional to an exponential function (log) of the dose. Other advantages of plotting log dose-response curves (DRC) are:

(i) A wide range of drug doses can be easily displayed on a graph.
(ii) Comparison between agonists and study of antagonists becomes easier. The log dose-response curve (DRC) can be characterized by its shape (slope and maxima) and position on the dose axis.

THERAPEUTIC EFFICACY

The ‘therapeutic efficacy’ or ‘clinical effectiveness’ is a composite attribute of a drug different from the foregoing pharmacological description of ‘potency’ and ‘efficacy’. It depends not only on the relative potency and efficacy of the drug, but on many pharmacokinetic and pathophysiological variables as well. It is often expressed in terms of (a) degree of benefit/relief afforded by the drug (in the recommended dose range) or (b) the success rate in achieving a defined therapeutic end point.

COMBINED EFFECT OF DRUGS

When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit synerg antagonism. The interaction may take place at pharmacokinetic level or at pharmacodynamic level.

SYNERGISM (Greek: Syn—together; ergon—work)

When the action of one drug is facilitated or increased by the other, they are said to be synergistic. In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together. Synergism can be:

(a) Additive The effect of the two drugs is in the same direction and simply adds up: effect of drugs A + B = effect of drug A + effect of drug B

(b) Supraadditive (potentiation) The effect of combination is greater than the individual effects of the components: effect of drug A + B > effect of drug A + effect of drug B

ANTAGONISM

When one drug decreases or abolishes the action of another, they are said to be antagonistic: effect of drugs A + B < effect of drug A + effect of drug B Usually in an antagonistic pair one drug is inactive as such but decreases the effect of the other. Depending on the mechanism involved, antagonism may be:

A Physical antagonism-

Based on the physical property of the drugs, e.g harcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

B Chemical antagonism

The two drugs react chemically and form an inactive product, e.g.

• KMnO4 oxidizes alkaloids—used for gastric lavage in poisoning.

• Tannins + alkaloids—insoluble alkaloidal tannate is formed.

• Chelating agents (BAL, Cal. disod. edetate) complex toxic metals (As, Pb).

• Nitrites form methaemoglobin which reacts with cyanide radical.

C Physiological/functional antagonism

The two drugs act on different receptors or by different mechanisms, but have opposite overt effects on the same physiological function, i.e. have pharmacological effects in opposite direction, e.g.

• Histamine and adrenaline on bronchial muscles and BP.

• Hydrochlorothiazide and triamterene on urinary K+ excretion.

• Glucagon and insulin on blood sugar level.

(d) Receptor antagonism

One drug (antagonist) blocks the receptor action of the other (agonist). This is a very important mechanism of drug action, because physiological signal molecules act through their receptors, blockade of which can produce specific and often profound pharmacological effects. Receptor antagonists are selective (relatively), i.e. an anticholinergic will oppose contraction of intestinal smooth muscle induced by cholinergic agonists, but not that induced by histamine Receptor antagonism can be competitive or noncompetitive.

THE THERAPEUTIC INDEX

(TI; also referred to as therapeutic ratio) is a quantitative measurement of the relative safety of a drug. It is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes toxicity. The related terms therapeutic window or safety window refer to a range of doses which optimize between efficacy and toxicity, achieving the greatest therapeutic benefit without resulting in unacceptable side-effects or toxicity.

Classically, in an established clinical indication setting of an approved drug, TI refers to the ratio of the dose of drug that causes adverse effects at an incidence/severity not compatible with the targeted indication (e.g. toxic dose in 50% of subjects, TD50) to the dose that leads to the desired pharmacological effect (e.g. efficacious dose in 50% of subjects, ED50). In contrast, in a drug development setting TI is calculated based on plasma exposure levels.

In the early days of pharmaceutical toxicology, TI was frequently determined in animals as lethal dose of a drug for 50% of the population (LD50) divided by the minimum effective dose for 50% of the population (ED50). Today, more sophisticated toxicity endpoints are used.

FACTORS MODIFYING DRUG ACTION

Variation in response to the same dose of a drug between different patients and even in the same patient on different occasions is a rule rather than exception. One or more of the following categories of differences among individuals are responsible for the variations in drug response:

(1) Individuals differ in pharmacokinetic handling of drugs: attain varying plasma/target site concentration of the drug. This is more marked for drugs disposed by metabolism (e.g. propranolol) than for drugs excreted unchanged (e.g. atenolol).
(2) Variations in number or state of receptors, coupling proteins or other components of response effectuation.

The factors modify drug action either:

(a) Quantitatively The plasma concentration and/or the action of the drug is increased or decreased. Most of the factors introduce this type of change and can be dealt with by adjustment of drug dosage.
(b) Qualitatively The type of response is altered, e.g. drug allergy or idiosyncrasy. This is less common but often precludes further use of that drug in the affected patient.

The various factors are discussed below—

1. **Body size** It influences the concentration of the drug attained at the site of action. The average adult dose refers to individuals of medium built.
2. **Age** The dose of a drug for children is often calculated from the adult dose.
3. **Sex** Females have smaller body size and require doses that are on the lower side of the range. Subjective effects of drugs may differ in females because of their mental makeup. Maintenance treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men.
4. **Species and race** There are many examples of differences in responsiveness to drugs among different species; rabbits are resistant to atropine, rats and mice are resistant to digitalis and rat is more sensitive to curare than cat. These differences are important while extrapolating results from experimental animals to man.

NEW DRUG DEVELOPMENT

In this era of bewildering new drug introduction and rapid attrition of older drugs, the doctor needs to have an overall idea of the manner in which new drugs are developed and marketed. Drug development now is a highly complex, tedious, competitive, costly and commercially risky process.

Approaches to drug discovery/ invention Exploration of natural sources Plants are the oldest source of medicines. Clues about these have been obtained from traditional systems of medicine prevalent in various parts of the world; Opium (morphine), Ephedra (ephedrine), Cinchona (quinine), curare (tubocurarine), belladonna (atropine), Quinghaosu (artemisinin) are the outstanding examples. Though animal parts have been used as cures since early times, it was physiological experiments performed in the 19th and early 20th century that led to introduction of some animal products into medicine, e.g. adrenaline, thyroxine, insulin, liver extract, antisera, etc. Few minerals (iron/calcium salts, etc.) are the other natural medicinal substances. The discovery of penicillin (1941) opened the flood-gates of a vast source—microorganisms—of a new kind of drugs (antibiotics). The use of microbes for production of vaccines is older than their use to produce antibiotics.

- **Random or targeted chemical synthesis** Synthetic chemistry made its debut in the 19th century and is now the largest source of medicines. Randomly synthesized compounds can be tested for a variety of pharmacological activities. Though some useful drugs (barbiturates, chlorpromazine) have been produced serendipitously by this approach, it has very low probability of hitting at the right activity in the right compound; rarely employed now.

- **Rational approach** This depends on sound physiological, biochemical, pathological knowledge and identification of specific target for drug action, such as H+ K+ ATPase for gastric acid suppression or glycoprotein IIa/IIIb receptor for platelet function inhibition.The drug is aimed at mitigating the derangement caused by the disease, e.g. levodopa was tried in parkinsonism based on the finding that the condition resulted from deficiency of dopamine in the striatum.

- **Combinatorial chemistry** Chemical groups are combined in a random manner to yield innumerable compounds and subjected to high-throughput screening on cells, genetically engineered microbes, receptors, enzymes, etc. in robotically controlled automated assay systems. Computerized analysis is used to identify the so called 'hits.' These compounds are then subjected to conventional tests. This new approach has vast potentials, but failure rates are high.

Preclinical studies After synthesizing/identifying a prospective compound, it is tested on animals to expose the whole pharmacological profile. Experiments are generally performed on a rodent (mouse, rat, guinea pig, hamster, rabbit) and then on a larger animal (cat, dog, monkey). As the evaluation progresses unfavourable compounds get rejected at each step, so that only a few out of thousands reach the stage when administration to man is considered.

The following types of tests are performed.

1. Screening tests These are simple and rapidly performed tests to indicate presence or absence of a particular pharmacodynamic activity that is sought for, e.g. analgesic or hypoglycaemic activity.

2. Tests on isolated organs, bacterial cultures, etc. These also are preliminary tests to detect specific activity, such as antihistaminic, antisecretory, vasodilator, antibacterial, etc.

3. Tests on animal models of human disease Such as kindled seizures in rats, spontaneously (genetically) hypertensive rats, experimental tuberculosis in mouse, alloxan induced diabetes in rat or dog, etc.

4. Confirmatory tests and analogous activities Compounds found active are taken up for detailed study by more elaborate tests which confirm and characterize the activity. Other related activities, e.g. antipyretic and anti-inflammatory activity in an analgesic are tested.

5. Systemic pharmacology Irrespective of the primary action of the drug, its effects on major organ systems such as nervous, cardiovascular, respiratory, renal, g.i.t are worked out. Mechanism of action, including additional mechanisms, e.g. α adrenergic blockade, calcium channel blockade, nitro-vasodilatation, etc. in a β adrenergic blocker antihypertensive, are elucidated.

6. Quantitative tests The dose-response relationship, maximal effect and comparative potency/efficacy with existing drugs is ascertained.

7. Pharmacokinetics The absorption, tissue distribution, metabolism, excretion, volume of distribution and halflife of the drug are quantified.

8. Toxicity tests The aim is to determine safety of the compound in at least 2 animal species, mostly mouse/rat and dog by oral and parenteral routes.

CLINICAL TRIALS

When a compound deserving trial in man is identified by animal studies, the regulatory authorities are approached who on satisfaction issue an 'investigational new drug' (IND) licence. The drug is formulated into a suitable dosage form and clinical trials are conducted in a logical phased manner. To minimize any risk, initially few subjects receive the drug under close supervision. Later, larger numbers are treated with only relevant monitoring.

The clinical studies are conventionally divided into 4 phases.

Phase I: Human pharmacology and safety

The first human administration of the drug is carried out by qualified clinical pharmacologists/ trained physicians in a setting where all vital functions are monitored and emergency/ resuscitative facilities are available. Subjects (mostly healthy volunteers, sometimes patients) are exposed to the drug one by one (total 20– 80 subjects), starting with the lowest estimated dose and increasing stepwise to achieve the effective dose.

Phase II: Therapeutic exploration and dose ranging

This is conducted by physicians who are trained as clinical investigators, and involve 100–500 patients selected according to specific inclusion and exclusion criteria. The primary aim is establishment of therapeutic efficacy, dose range and ceiling effect in a controlled setting. Tolerability and pharmacokinetics are studied as extension of phase I. The study is mostly controlled and randomized, and may be blinded or open label. It is generally carried out at 2–4 centres. The candidate drug may get dropped at this stage if the desired level of clinical efficacy is not obtained.

Phase III: Therapeutic confirmation/ comparison

Generally these are randomized double blind comparative trials conducted on a larger patient population (500–3000) by several physicians (usually specialists in treating the target disease) at many centres. The aim is to establish the value of the drug in relation to existing therapy. Safety and tolerability are assessed on a wider scale, while pharmacokinetic studies may be conducted on some of the participants to enlarge the population base of pharmacokinetic data. Indications are finalized and guidelines for therapeutic use are formulated. A 'new drug application' (NDA) is submitted to the licencing authority, who if convinced give marketing permission.

Phase IV: Postmarketing surveillance/ studies

After the drug has been marketed for general use, practicing physicians are identified through whom data are collected on a structured proforma about the efficacy, acceptability and adverse effects of the drug (similar to prescription event monitoring). Patients treated in the normal course form the study population: numbers therefore are much larger. Uncommon/idiosyncratic adverse effects, or those that occur only after long-term use and unsuspected drug interactions are detected at this stage. Patterns of drug utilization and additional indications may emerge from the surveillance data.

PHARMACOVIGILANCE

Pharmacovigilance has been defined by the WHO (2002) as the 'science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.' The information generated by pharmacovigilance is useful in educating doctors about ADRs and in the official regulation of drug use. Its main purpose is to reduce the risk of drug-related harm to the patient. It has an important role in the rational use of medicines, as it provides the basis for assessing safety of medicines. The activities involved in pharmacovigilance are:

a. Postmarketing surveillance and other methods of ADR monitoring such as voluntary reporting by doctors (e.g. yellow card system of UK), prescription event monitoring, computerized medical record linkage and other cohort/case control studies as well as anecdotal case reports by doctors.
b. Dissemination of ADR data through 'drug alerts', 'medical letters,' advisories sent to doctors by pharmaceuticals and regulatory agencies (such as FDA in USA, committee on safety of medicines in UK).
c. Changes in the labelling of medicines indicating restrictions in use or statuary warnings, precautions, or even withdrawal of the drug, by the regulatory decision making authority.

ADVERSE DRUG REACTION

For the purposes of detecting and quantifying only those adverse effects of a drug which are of some import and occur in ordinary therapeutic setting, the term adverse drug reaction (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'. This definition excludes trivial or expected side effects and poisonings or overdose.

Another term 'adverse drug event' (ADE) has been used to mean 'any untoward medical occurrence that may present during treatment with a medicine, but which does not necessarily have a causal relationship with the treatment'. The idea is to record all adverse events first, and look for causality only while analyzing pooled data.

Adverse effects may develop promptly or only after prolonged medication or even after stoppage of the drug. Adverse effects are not rare; an incidence of 10–25% has been documented in different clinical settings. They are more common with multiple drug therapy and in the elderly. Adverse effects have been classified in many ways. One may divide them into: Predictable (Type A or Augmented) reactions (mechanism based adverse reactions) These are based on the pharmacological properties of the drug, which means that they are augmented, but qualitatively normal response to the drug; include side effects, toxic effects and consequences of drug withdrawal. They are more common, dose related and mostly preventable and reversible. Unpredictable (Type B or Bizarre) reactions These are based on peculiarities of the patient and not on drug's known actions; include allergy and idiosyncrasy. They are less common, often non-dose related, generally more serious and require withdrawal of the drug. Some of these reactions can be predicted and prevented if their genetic basis is known and suitable test to characterize the individual's phenotype is performed. Severity of adverse drug reactions has been graded as: Minor: No therapy, antidote or prolongation of hospitalization is required. Moderate: Requires change in drug therapy, specific treatment or prolongs hospital stay by atleast one day. Severe: Potentially life-threatening, causes permanent damage or requires intensive medical treatment. Lethal: Directly or indirectly contributes to death of the patient.

DRUG INTERACTION

A drug interaction has occurred when the administration of one drug alters the clinical effects of another. The result may be an increase or decrease in either the beneficial or harmful effects of the second agent. Although the number of potential interacting drug combinations is very large only a small number are relevant in clinical practice.

Harmful drug interactions are most likely to occur when the affected drug has a:

- *Low therapeutic index* meaning that only a small increase in plasma concentration may cause toxic effects
- *Steep dose-response curve* meaning that a small change in plasma concentration leads to a significant increase in pharmacodynamic effect (where a small increase in dose results in a large increase in plasma level)
- *High first-pass metabolism* because these are drugs that are extensively metabolised in the liver or gastrointestinal tract and are therefore sensitive to the effects of metabolic inhibition or induction

- *Single mechanism of elimination* (e.g. renal clearance, cytochrome metabolism) meaning that the interacting drug can cause a significant increase in plasma concentration.

Drug interection Absorption

Absorption interactions involve changes in either the rate or extent of absorption. The rate of absorption of most drugs is dependent on gastric emptying into the small bowel. Drugs that either delay (e.g. anticholinergic drugs) or enhance (e.g. prokinetic drugs) the rate at which this occurs will influence the rate of rise in plasma concentration but not the total amount of drug absorbed. The extent of absorption can be influenced by second drugs that bind to form insoluble complexes or chelates (e.g. aluminium containing antacids binding with ciprofloxacin). Drug transport systems, notably the P-glycoprotein (the product of the multidrug resistance gene), are responsible for limiting or enhancing absorption of drugs. It is very likely that these will be the site of drug-drug interactions although most are uncharacterised.

Drug interection Distribution

Distribution interactions occur when drugs are extensively protein-bound and the co-administration of a second can displace it to the non-bound active form. This increases the amount of (unbound) drug available to cause an effect. For example, diazepam displaces phenytoin from plasma proteins, resulting in an increased plasma concentration of free phenytoin and an increased risk of toxicity. The effects of protein displacement are usually short-lived because the metabolism of the affected drug usually increases in parallel with the increased free drug concentration. Distribution interactions can however be significant for drugs that have extremely rapid distribution or narrow therapeutic indices, such as lithium or digoxin.

Drug interection Excretion

Excretion interactions primarily involve changes in renal excretion. This might be due to drug-induced reduction in glomerular filtration rate (e.g. diuretic-induced dehydration, ACE inhibitors, NSAIDs). This can reduce the clearance and increase the plasma concentration of many drugs, including some with a low therapeutic index (e.g. digoxin, lithium, aminoglycoside antibiotics). Less commonly, interactions may be due to competition for a common tubular organic anion transporters (e.g. methotrexate excretion may be inhibited by competition with NSAIDs). In some cases this kind of interaction can be used for therapeutic benefit (e.g. probenecid prolongs the half life of penicillin be competing for tubular excretion). The likelihood of clinically significant excretion interactions increases if a patient has renal impairment.

Drug interection Metabolism

Many drugs rely on metabolism by different isoenzymes of cytochrome P450 (CYP) in the liver, especially 3A, 2D6, 2C9, 2C19, and 1A2. Interacting drugs have the potential to either increase the rate of metabolism by inducing the formation of more CYP isoenzyme or decrease metabolism by inhibiting isoenzyme activity. Enzyme inducers (*e.g.* phenytoin, rifampicin) generally reduce plasma concentrations although may enhance conversion of a pro-drug to its active form. Enzyme inhibitors (*e.g.* clarithromycin, cimetidine, grapefruit juice) have the opposite effect. Enzyme induction effects usually take at least a few days to manifest because of the need to synthesise new CYP enzyme. In contrast, the effects of enzyme inhibition may be rapid with the affected drug quickly reaching a new higher steady state concentration.