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BRANCHES OF CLINICAL PHARMACOLOGY – A REVIEW

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ABSTRACT

Clinical pharmacology connects the gap between medical practice and laboratory science. The main objective is to promote the safety of prescription, maximise the drug effects and minimise the side effects. It is important that there be association with pharmacists skilled in areas of drug information, medication safety and other aspects of pharmacy practice related to clinical pharmacology.

Keywords: Drug Information, Medication Safety, Pharmacy Practice, Clinical Pharmacology.

INTRODUCTION

Clinical pharmacology is the science of drugs and their clinical use. It is underpinned by the basic science of pharmacology, with added focus on the application of pharmacological principles and methods in the real world. It has a broad scope, from the discovery of new target molecules, to the effects of drug usage in whole populations.

Clinical pharmacologists usually have a rigorous medical and scientific training which enables them to evaluate evidence and produce new data through well designed studies. Clinical pharmacologists must have access to enough outpatients for clinical care, teaching and education, and research as well be supervised by medical specialists. Their responsibilities to patients include, but are not limited to analyzing adverse drug effects, therapeutics, and toxicology including reproductive toxicology, cardiovascular risks, perioperative drug management and psychopharmacology.

In addition, the application of genetic, biochemical, or virotherapeutical techniques has led to a clear appreciation of the mechanisms involved in drug action [1].

Branches

Pharmacodynamics - finding out what drugs do to the body and how. This includes not just the cellular and molecular aspects, but also more relevant clinical measurements. For example, not just the biology of salbutamol, a beta2-adrenergic receptor agonist, but the peak flow rate of both healthy volunteers and real patients.

- Pharmacokinetics - what happens to the drug while in the body. This involves the body systems for handling the drug, usually divided into the following classification:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion.
- Rational Prescribing - using the right medication, at the right dose, using the right route and frequency of administration for the patient, and stopping the drug appropriately.
- Adverse Drug Effects
- Toxicology
- Drug interactions
- Drug development - usually culminating in some form of clinical trial.

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Pharmacodynamics

Pharmacodynamics is the study of the biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect. One dominant example is drug-receptor interactions as modeled by

$$L + R \rightleftharpoons L \cdot R$$

where L=ligand (drug), R=receptor (attachment site), reaction dynamics that can be studied mathematically through tools such as free energy maps. Pharmacodynamics is often summarized as the study of what a drug does to the body, whereas pharmacokinetics is the study of what the body does to a drug. Pharmacodynamics is sometimes abbreviated as "PD", while pharmacokinetics can be referred to as "PK".

Effects on the body

The majority of drugs either (a) mimic or inhibit vital processes of endo- or ectoparasites and microbial organisms.

There are 7 main drug actions:

- stimulating action through direct receptor agonism and downstream effects
- depressing action through direct receptor agonism and downstream effects (ex.: inverse agonist)
- blocking/antagonizing action (as with silent antagonists), the drug binds the receptor but does not activate it
- stabilizing action, the drug seems to act neither as a stimulant or as a depressant (ex.: some drugs possess receptor activity that allows to stabilize general receptor activation, like buprenorphine in opioid dependent individuals or aripiprazole in schizophrenia, all depending on the dose and the recipient)
- exchanging/replacing substances or accumulating them to form a reserve (ex.: glycogen storage)
- direct beneficial chemical reaction as in free radical scavenging
- direct harmful chemical reaction which might result in damage or destruction of the cells, through induced toxic or lethal damage (cytotoxicity or irritation)

Desired activity

The desired activity of a drug is mainly due to one of the following:

- Cellular membrane disruption
- Chemical reaction with downstream effects
- Interaction with enzyme proteins
- Interaction with structural proteins
- Interaction with carrier proteins
- Interaction with ion channels
- Ligand binding to receptors:
  - Hormone receptors
  - Neuromodulator receptors
  - Neurotransmitter receptors

General anesthetics were once thought to work by disordering the neural membranes, thereby altering the Na^+ influx. Antacids and chelating agents combine chemically in the body. Enzyme-substrate binding is a way to alter the production or metabolism of key endogenous chemicals, for example aspirin irreversibly inhibits the enzyme prostaglandin synthetase (cyclooxygenase) thereby preventing inflammatory response. Colchicine, a drug for gout, interferes with the function of the structural protein tubulin, while Digitalis, a drug still used in heart failure, inhibits the activity of the carrier molecule, Na-K-ATPase pump. The widest class of drugs act as ligands which bind to receptors which determine cellular effects. Upon drug binding, receptors can elicit their normal action (agonist), blocked action (antagonist), or even action opposite to normal (inverse agonist).

In principle, a pharmacologist would aim for a target plasma concentration of the drug for a desired level of response. In reality, there are many factors affecting this goal. Pharmacokinetic factors determine peak concentrations, and concentrations cannot be maintained with absolute consistency because of metabolic breakdown and excretory clearance. Genetic factors may exist which would alter metabolism or drug action itself, and a patient's immediate status may also affect indicated dosage.

Undesirable effects

Undesirable effects of a drug include:

- Increased probability of cell mutation (carcinogenic activity)
- A multitude of simultaneous assorted actions which may be deleterious
- Interaction (additive, multiplicative, or metabolic)
- Induced physiological damage, or abnormal chronic conditions

Therapeutic window

The therapeutic window is the amount of a medication between the amount that gives an effect (effective dose) and the amount that gives more adverse effects than desired effects. For instance, medication with a small pharmaceutical window must be administered with care and control, e.g. by frequently measuring blood concentration of the drug, since it easily loses effects or gives adverse effects.

Receptor binding

The binding of ligands (drug) to receptors is governed by the law of mass action which relates the large-scale status to the rate of numerous molecular processes. The rates of formation and un-formation can be used to determine the equilibrium concentration of bound

receptors. The equilibrium dissociation constant is defined by:

$$L + R \leftrightarrow L \cdot R \qquad K_d = \frac{[L][R]}{[L \cdot R]}$$

where L=ligand, R=receptor, square brackets [] denote concentration. The fraction of bound receptors is Semi-log plots of two agonists with different K_d. The blue curve represents the ligand with greater potency.

$$Fraction\ Bound = \frac{[L \cdot R]}{[R] + [L \cdot R]} = \frac{1}{1 + \frac{K_d}{[L]}}$$

This expression is one way to consider the effect of a drug, in which the response is related to the fraction of bound receptors. The fraction of bound receptors is known as occupancy. The relationship between occupancy and pharmacological response is usually non-linear. This explains the so called receptor reserve phenomenon i.e. the concentration producing 50% occupancy is typically higher than the concentration producing 50% of maximum response.

Often the response is determined as a function of log[L] to consider many orders of magnitude of concentration. However, there is no biological or physical theory which relates effects to the log of concentration. It is just convenient for graphing purposes. It is useful to note that 50% of the receptors are bound when $[L]=K_d$.

The graph shown represents the conc-response for two hypothetical receptor agonists, plotted in a semi-log fashion. The curve toward the left represents a higher potency (potency arrow does not indicate direction of increase) since lower concentrations are needed for a given response. The effect increases as a function of concentration.

Multicellular pharmacodynamics

The concept of pharmacodynamics has been expanded to include Multicellular Pharmacodynamics (MCPD). MCPD is the study of the static and dynamic properties and relationships between a set of drugs and a dynamic and diverse multicellular 4 dimensional organization. It is the study of the workings of a drug on a minimal multicellular system (mMCS), both in vivo and in silico. Networked Multicellular Pharmacodynamics (Net-MCPD) further extends the concept of MCPD to model regulatory genomic networks together with signal transduction pathways, as part of a complex of interacting components in the cell [2].

Pharmacokinetics

Pharmacokinetics, sometimes abbreviated as PK, (from Ancient Greek pharmakon "drug" and kinetikos "to do with motion"; see chemical kinetics) is a branch of pharmacology dedicated to the determination of the fate of substances administered externally to a living organism. The substances of interest include pharmaceutical agents, hormones, nutrients, and toxins.

Pharmacokinetics is often studied in conjunction with pharmacodynamics. Pharmacokinetics includes the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body (e.g. by metabolic enzymes such as CYP or UGT enzymes) and the effects and routes of excretion of the metabolites of the drug.

ADME

Pharmacokinetics is divided into several areas including the extent and rate of absorption, distribution, metabolism and excretion. This is commonly referred to as the ADME scheme:

- **A**bsorption - the process of a substance entering the blood circulation.
- **D**istribution - the dispersion or dissemination of substances throughout the fluids and tissues of the body.
- **M**etabolism (or Biotransformation) - the irreversible transformation of parent compounds into daughter metabolites.
- **E**xcretion (or Elimination) - the elimination of the substances from the body. In rare cases, some drugs irreversibly accumulate in body tissue.

Pharmacokinetics describes how the body affects a specific drug after administration. Pharmacokinetic properties of drugs may be affected by elements such as the site of administration and the dose of administered drug. These may affect the absorption rate.

A fifth process, **Liberation** has been highlighted as playing an important role in pharmacokinetics:

- Liberation - the process of release of drug from the formulation.

Hence **LADME** may sometimes be used in place of **ADME** in reference to the core aspects of pharmacokinetics.

Drugs injected intravenously are removed from the plasma through two primary mechanisms:

(1) Distribution to body tissues and

(2) metabolism + excretion of the drugs. The resulting decrease of the drug's plasma concentration follows a biphasic pattern.

Alpha phase: An initial phase of rapid decrease in plasma concentration. The decrease is primarily attribute to drug distribution from the central compartment (circulation) into the peripheral compartments (body tissues). This phase

ends when equilibrium of drug concentration is established between the central and peripheral compartments.
Beta phase: A phase of gradual decrease in plasma concentration after the alpha phase. The decrease is primarily attributed to drug metabolism and excretion [3].

Analysis

Pharmacokinetic analysis is performed by noncompartmental (model independent) or compartmental methods. Noncompartmental methods estimate the exposure to a drug by estimating the area under the curve of a concentration-time graph. Compartmental methods estimate the concentration-time graph using kinetic models. Compartment-free methods are often more versatile in that they do not assume any specific compartmental model and produce accurate results also acceptable for bioequivalence studies.

Noncompartmental analysis

Noncompartmental PK analysis is highly dependent on estimation of total drug exposure. Total drug exposure is most often estimated by area under the curve (AUC) methods, with the trapezoidal rule (numerical integration) the most common method. Due to the dependence on the length of 'x' in the trapezoidal rule, the area estimation is highly dependent on the blood/plasma sampling schedule. That is, the closer time points are, the closer the trapezoids reflect the actual shape of the concentration-time curve [4].

Compartmental analysis

Compartmental PK analysis uses kinetic models to describe and predict the concentration-time curve. PK compartmental models are often similar to kinetic models used in other scientific disciplines such as chemical kinetics and thermodynamics. The advantage of compartmental over some noncompartmental analyses is the ability to predict the concentration at any time. The disadvantage is the difficulty in developing and validating the proper model. Compartment-free modeling based on curve stripping does not suffer this limitation. The simplest PK compartmental model is the one-compartmental PK model with IV bolus administration and first-order elimination. The most complex PK models (called PBPK models) rely on the use of physiological information to ease development and validation.

Bioanalytical methods

Bioanalytical methods are necessary to construct a concentration-time profile. Chemical techniques are employed to measure the concentration of drugs in biological matrix, most often plasma. Proper bioanalytical methods should be selective and sensitive. For example microscale thermophoresis can be used to quantify how the biological matrix/liquid affects the affinity of a drug to its target.

Mass spectrometry

Pharmacokinetics is often studied using mass spectrometry because of the complex nature of the matrix (often plasma or urine) and the need for high sensitivity to observe concentrations after a low dose and a long time period. The most common instrumentation used in this application is LC-MS with a triple quadrupole mass spectrometer. Tandem mass spectrometry is usually employed for added specificity. Standard curves and internal standards are used for quantitation of usually a single pharmaceutical in the samples. The samples represent different time points as a pharmaceutical is administered and then metabolized or cleared from the body. Blank samples taken before administration are important in determining background and insuring data integrity with such complex sample matrices. Much attention is paid to the linearity of the standard curve; however it is not uncommon to use curve fitting with more complex functions such as quadratics since the response of most mass spectrometers is less than linear across large concentration ranges.

There is currently considerable interest in the use of very high sensitivity mass spectrometry for microdosing studies, which are seen as a promising alternative to animal experimentation.

Population pharmacokinetics

Population pharmacokinetics is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. Certain patient demographic, pathophysiological, and therapeutical features, such as body weight, excretory and metabolic functions, and the presence of other therapies, can regularly alter dose-concentration relationships. For example, steady-state concentrations of drugs eliminated mostly by the kidney are usually greater in patients suffering from renal failure than they are in patients with normal renal function receiving the same drug dosage. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be appropriately modified [5].

Medical prescription

A prescription (℞) is a health-care program implemented by a physician or other medical doctors in the form of instructions that govern the plan of care for an individual patient. Prescriptions may include orders to be performed by a patient, caretaker, nurse, pharmacist or other therapist. Commonly, the term prescription is used to mean an order to take certain medications. Prescriptions have legal implications, as they may indicate that the

prescriber takes responsibility for the clinical care of the patient and in particular for monitoring efficacy and safety. As medications have increasingly become pre–packaged manufactured products and medical practice has become more complex, the scope of meaning of the term "prescription" has broadened to also include clinical assessments, laboratory tests, and imaging studies relevant to optimizing the safety or efficacy of medical treatment.

Prescriptions are handwritten on preprinted prescription forms that are assembled into pads, or alternatively printed onto similar forms using a computer printer or are in an electronic format. Preprinted on the form is text that identifies the document as a prescription, the name and address of the prescribing provider and any other legal requirement such as a registration number (e.g. DEA Number in the United States). Unique for each prescription is the name of the patient. In the United Kingdom and Ireland, the patient's name and address must also be recorded. Each prescription is dated and some jurisdictions may place a time limit on the prescription. There is the specific "recipe" of the medication and the directions for taking it.

℞ is a symbol meaning "prescription". It is sometimes transliterated as "R_x" or just "Rx". This symbol originated in medieval manuscripts as an abbreviation of the Late Latin verb recipe, the imperative form of recipere, "to take" or "take thus". Literally, the Latin word recipe means simply "Take...." and medieval prescriptions invariably began with the command to "take" certain materials and compound them in specified ways. Today, when a medical practitioner writes a prescription beginning with "℞", he or she is completing the command.

Folk theories about the origin of the symbol ℞ note its similarity to the Eye of Horus, or to the ancient symbol for Zeus or Jupiter, (♃), gods whose protection may have been sought in medical contexts.

The word "prescription", from "pre-" ("before") and "script" ("writing, written"), refers to the fact that the prescription is an order that must be written down before a compound drug can be prepared. Those within the industry will often call prescriptions simply "scripts".

The fact that a prescription instructs someone to "take" rather than "give" is not a trivial distinction, but makes clear it is directed at the patient, and is not directly an instruction to anyone else. In certain states medical marijuana legislation has been drafted calling for a health care professional's written or oral "recommendation", in the belief that a written one would be legally distinguishable from a prescription, but since written advice to a patient is what a prescription is, that belief is mistaken. Jurisdictions may adopt a statutory definition of "prescription" which is applicable as a term of art only to the operation of that statute (see below about prescriptions that may legally be filled with prescription-only items), but the general legal definition of the word is this broad one [6].

Contents

Both pharmacists and prescribers are regulated professions in most jurisdictions. A prescription as a communications mechanism between them is also regulated and is a legal document.

Regulations may define what constitutes a prescription, the contents and format of the prescription and how prescriptions are handled and stored by the pharmacist. Many jurisdictions will now allow faxed or phone prescriptions containing the same information. Exhibit A below illustrates the legal definition of a prescription.

Drug companies use direct-to-prescriber advertising in an effort to convince prescribers to dispense as written with brand-name products rather than generic drugs.

Many brand name drugs have less expensive generic drug substitutes that are therapeutically and biochemically equivalent. Prescriptions will also contain instructions on whether the prescriber will allow the pharmacist to substitute a generic version of the drug. This instruction is communicated in a number of ways.

In some jurisdictions, the preprinted prescription contains two signature lines: one line has "dispense as written" printed underneath; the other line has "substitution permitted" underneath. Some have a preprinted box "dispense as written" for the prescriber to check off (but this is easily checked off by anyone with access to the prescription). Other jurisdictions the protocol is for the prescriber to handwrite one of the following phrases: "dispense as written", "DAW", "brand necessary", "do not substitute", "no substitution", "medically necessary", "do not interchange". In other jurisdictions may they use completely different languages, never mind a different formula of words. In some jurisdictions, it may be a legal requirement to include the age of child on the prescription. For pediatric prescriptions some advise the inclusion of the age of the child if the patient is less than twelve and the age and months if less than five. (In general, including the age on the prescription is helpful.) Adding the weight of the child is also helpful.

Prescriptions often have a "label" box. When checked, the pharmacist is instructed to label the medication. When not checked, the patient only receives

instructions for taking the medication and no information about the prescription itself.
Some prescribers further inform the patient and pharmacist by providing the indicator for the medication; i.e. what is being treated. This assists the pharmacist in checking for errors as many common medications can be used for multiple medical conditions.

Some prescriptions will specify whether and how many "repeats" or "refills" are allowed; that is whether the patient may obtain more of the same medication without getting a new prescription from the medical practitioner. Regulations may restrict some types of drugs from being refilled.

In group practices, the preprinted portion of the prescription may contain multiple prescribers' names. Prescribers typically circle themselves to indicate who is prescribing or there may be a checkbox next to their name [7].

Handling

When filled by a pharmacist, as a matter of business practice, the pharmacist may write certain information right on the prescription. This may also be mandated by legislation (see Exhibit D). Information such as the actual manufacturer of the drug and the date the medication was dispensed may be written right onto the prescription. Legislation may require the pharmacist sign the prescription. In computerized pharmacies, all such information is printed and stapled to the prescription. Sometimes such information is printed onto labels and the labels affixed right onto the prescription.

When filled by the pharmacist, prescriptions are typically assigned a "prescription number" (often abbreviated "Rx#" in the US) that is unique to the pharmacy that filled the prescription. The prescription number is written right on the prescription by the pharmacist. The prescription number has the practical purpose of uniquely identifying the prescription later on while filed (both manual and electronic). The prescription number is also put on the label on the dispensed medication. The patient may be required to reference the prescription number for refills and drug insurance claims. There may also be a legal requirement for prescription numbers for subsequent identification purposes.

As a legal document, some jurisdictions will mandate the archiving of the original paper prescription in the pharmacy. Often the patient cannot take the original prescription with them. Some jurisdictions may entitle patients to a copy. The retention period varies but can be as long as ten years (requirement of all prescriptions billed to a Medicare Part D plan.) See Exhibit B for sample legislation governing the archiving of prescriptions. Once the retention period has passed, privacy legislation may dictate what can be done with the original paper prescription. Legislation may also dictate what happens to the prescriptions if the pharmacy closes or is sold. For example, if the pharmacy goes out of business, the pharmacist may be required to return the prescription to the patient, to the next closest pharmacy or to the governing body for pharmacists.

Prescriptions for non-narcotic drugs may also be "transferred" from one pharmacy to another for subsequent repeats to be dispensed from another pharmacy. The physical piece of paper that is the prescription is not transferred, but all the information on it is transferred from one pharmacy to another. Legislation may dictate the protocol by which the transfer occurs and whether the transfer needs to be noted on the original paper prescription.
It is estimated that three billion prescriptions were written in the United States in 2002. This number grew from 1.5 billion in 1989 and is expected to continue to grow.

Rx security – forgeries and prevention

Prescriptions are sometimes forged because many narcotics are cheaper and safer as prescription drugs than as street drugs. Forgery takes many forms: Prescription pads are sometimes stolen, amounts may be altered on legitimate prescriptions, call back numbers may be falsified and phoned or faxed prescriptions faked.

To make photocopying prescriptions more difficult, some medical practitioners use prescription pads that contain security measures similar to those used on bank checks. These security measures may be mandated by law—see Exhibit C for sample legal specifications. Legislation may mandate that only certain printers may print prescriptions. New Jersey, for example, requires that only state approved printers may be used to print official "New Jersey Prescription Blanks. (See Exhibit E.) Prescribers can make it more difficult to forge dosages and quantities by writing out numbers in words. Again, this may be mandated by law.

Some jurisdictions help control stolen prescriptions by requiring special "triplicate prescriptions" for certain classes of drugs. Blank triplicates are only available from the regulating agency and are individually numbered. The medical practitioner retains a copy, the second and third copies are given to the patient to give to the pharmacist. The pharmacist retains the second copy and the third copy is submitted to the regulating agency. The regulating agency can issue lists of forged prescriptions that pharmacists can check. In this example, the prescription's validity is further limited to 72 hours from issuance. California has recently replaced triplicate forms with new forms that are impossible to photocopy or

fax: the background is printed with repetitions of the word void in a color that shows up as black on a photocopy. States have various laws making theft of prescription blanks or forgery of prescriptions criminal offenses and/or providing special treatment for these offenses. When forgery is suspected, pharmacists will call the medical practitioner to verify the prescription. Forged prescriptions are no longer considered medical documents and doctor-patient confidentiality rules no longer apply.

Writing prescriptions

Any jurisdiction that allows freedom of written communication generally must therefore allow anybody to write a prescription to anybody, inasmuch as the prescription itself is just written advice. Therefore "who can write prescriptions" will be explained below as shorthand for "whose prescriptions may legally be filled with items restricted to dispensing via the order of certain persons".

National or local (i.e. state or provincial) legislation governs who can write a prescription. In North America, physicians (either M.D. or D.O.) have the broadest prescriptive authority. All 50 States and the District of Columbia allow licensed certified Physician Assistants (PAs) prescription authority (with some limitations to controlled substances). All 50 States allow registered certified Nurse Practitioners and other advanced-practice nurses (such as certified nurse-midwives) prescription power (with some states including limitations to controlled substances). Many other healthcare professions also have prescriptive authority related to their area of practice. Veterinarians, dentists, and podiatrists have prescribing power in all 50 states and the District of Columbia. Clinical pharmacists are allowed to prescribe in some states through the use of a drug formulary or collaboration agreements. Florida Pharmacists can write prescriptions for a limited set of drugs. In all states, optometrists prescribe medications to treat certain eye diseases, and also issue spectacle and contact lens prescriptions for corrective eyewear. Several states have passed RxP legislation, allowing clinical psychologists (PhD's or PsyD's) who are registered as medical psychologists and have also undergone specialized training in script-writing to prescribe drugs to treat emotional and mental disorders. Rarely, people who practice the non-medical intervention of chiropractic may have the ability to write a prescription, but then only under certain conditions [8].

Legibility

Prescriptions, when handwritten, are notorious for being often illegible. In the US, medical practitioners' sloppy handwriting kills more than 7,000 people annually, according to a July 2006 report from the National Academies of Science's Institute of Medicine (IOM). Historically, physicians used Latin words and abbreviations to convey the entire prescription to the pharmacist. Today, many of the abbreviations are still widely used and must be understood to interpret prescriptions. At other times, even though some of the individual letters are illegible, the position of the legible letters and length of the word is sufficient to distinguish the medication based on the knowledge of the pharmacist. When in doubt, pharmacists call the medical practitioner. Some jurisdictions have legislated legible prescriptions (e.g. Florida). Some have advocated the elimination of handwritten prescriptions altogether and computer printed prescriptions are becoming increasingly common in some places.

Conventions for avoiding ambiguity

Over the years, prescribers have developed many conventions for prescription-writing, with the goal of avoiding ambiguities or misinterpretation. These include:

- Careful use of decimal points to avoid ambiguity:

✓ Avoiding unnecessary decimal points: a prescription will be written as 5 mL instead of 5.0 mL to avoid possible misinterpretation of 5.0 as 50.

✓ Always using zero prefix decimals: e.g. 0.5 instead of .5 to avoid misinterpretation of .5 as 5.

✓ Avoiding trailing zeros on decimals: e.g. 0.5 instead of .50 to avoid misinterpretation of .50 as 50.

- "mL" is used instead of "cc" or "cm^3" even though they are technically equivalent to avoid misinterpretation of 'c' as '0' or the common medical abbreviation for "with" (the Latin "cum"), which is written as a 'c' with a bar above the letter. Further, cc could be misinterpreted as "c.c.", which is an uncommonly used abbreviation for "take with meals" (the Latin "cum cibo").
- Directions written out in full in English (although some common Latin abbreviations are listed below).
- Quantities given directly or implied by the frequency and duration of the directions.
- Where the directions are "as needed", the quantity should always be specified.
- Where possible, usage directions should specify times (7 am, 3 pm, 11 pm) rather than simply frequency (three times a day) and especially relationship to meals for orally consumed medication.
- The use of permanent ink.
- Avoiding unspecified prn or "as needed" instructions—instead, specific limits and indicators are provided e.g. "every 3 hours prn pain."
- For refills, the minimum duration between repeats and number of repeats should be specified.
- Providing the indication for all prescriptions even when obvious to the prescriber, so that the pharmacist may identify possible errors.
- Avoiding units such as "teaspoons" or "tablespoons."

- Writing out numbers as words and numerals ("dispense #30 (thirty)") as in a bank draft or cheque.
- The use of apothecary/avoirdupois units and symbols of measure -- pints (**O**), ounces (℥), drams (ʒ), scruples (℈), grains (**gr**), and minims (♏) -- is discouraged given the potential for confusion. For example, the abbreviation for a grain ("gr") can be confused with the gram, abbreviated g, and the symbol for minims (♏), which looks almost identical to an 'm', can be confused with micrograms or metres. Also, the symbols for ounce (℥) and dram (ʒ) can easily be confused with the numeral '3', and the symbol for pint (O) can be easily read as a '0'. Given the potential for errors, metric equivalents should always be used.
- The use of the degree symbol (°), which is commonly used as an abbreviation for hours (e.g., "q 2-4°" for every 2 – 4 hours), should not be used, since it can be confused with a '0'. Further, the use of the degree symbol for primary, secondary, and tertiary (1°, 2°, and 3°) is discouraged, since the former could be confused with quantities (i.e. 10, 20 and 30, respectively).

In medicine, an **adverse effect** is a harmful and undesired effect resulting from a medication or other intervention such as surgery.

An adverse effect may be termed a "side effect", when judged to be secondary to a main or therapeutic effect. If it results from an unsuitable or incorrect dosage or procedure, this is called a medical error and not a complication. Adverse effects are sometimes referred to as "iatrogenic" because they are generated by a physician/treatment. Some adverse effects only occur only when starting, increasing or discontinuing a treatment.
Using a drug or other medical intervention which is contraindicated may increase the risk of adverse effects. Adverse effects may cause complications of a disease or procedure and negatively affect its prognosis. They may also lead to non-compliance with a treatment regimen.

The harmful outcome is usually indicated by some result such as morbidity, mortality, alteration in body weight, levels of enzymes, loss of function, or as a pathological change detected at the microscopic, macroscopic or physiological level. It may also be indicated by symptoms reported by a patient. Adverse effects may cause a reversible or irreversible change, including an increase or decrease in the susceptibility of the individual to other chemicals, foods, or procedures, such as drug interactions.

In clinical trials, a distinction is made between adverse events (AEs) and serious adverse events (SAEs). Generally, any event which causes death, permanent damage, birth defects, or requires hospitalization is considered an SAE.[1] The results of these trials are often included in the labeling of the medication to provide information both for patients and the prescribing physicians.

Adverse effects of medical procedures

Surgery may have a number of undesirable or harmful effects, such as infection, hemorrhage, inflammation, scarring, loss of function, or changes in local blood flow. They can be reversible or irreversible, and a compromise must be found by the physician and the patient between the beneficial or life-saving consequences of surgery versus its adverse effects. For example, a limb may be lost to amputation in case of untreatable gangrene, but the patient's life is saved. Presently, one of the greatest advantages of minimally invasive surgery, such as laparoscopic surgery, is the reduction of adverse effects.

Other nonsurgical physical procedures, such as high-intensity radiation therapy, may cause burns and alterations in the skin. In general, these therapies try to avoid damage to healthy tissues while maximizing the therapeutic effect.

Vaccination may have adverse effects due to the nature of its biological preparation, sometimes using attenuated pathogens and toxins. Common adverse effects may be fever, malaise and local reactions in the vaccination site. Very rarely, there is a serious adverse effect, such as eczema vaccinatum, a severe, sometimes fatal complication which may result in persons who have eczema or atopic dermatitis.

Diagnostic procedures may also have adverse effects, depending much on whether they are invasive, minimally invasive or noninvasive. For example, allergic reactions to radiocontrast materials often occur, and a colonoscopy may cause the perforation of the intestinal wall.

Adverse effects of drugs

Adverse effects can occur as a collateral or side effect of many interventions, but they are particularly important in pharmacology, due to its wider, and sometimes uncontrollable, use by way of self-medication. Thus, responsible drug use becomes an important issue here. Adverse effects, like therapeutic effects of drugs, are a function of dosage or drug levels at the target organs, so they may be avoided or decreased by means of careful and precise pharmacokinetics, the change of drug levels in the organism in function of time after administration.

Adverse effects may also be caused by drug interaction. This often occurs when patients fail to inform their physician and pharmacist of all the medications they are taking, including herbal and dietary supplements. The new medication may interact agonistically or

antagonistically (potentiate or decrease the intended therapeutic effect), causing significant morbidity and mortality around the world. Drug-drug and food-drug interactions may occur, and so-called "natural drugs" used in alternative medicine can have dangerous adverse effects. For example, extracts of St John's wort (Hypericum perforatum), a phytotherapic used for treating mild depression are known to cause an increase in the cytochrome P450 enzymes responsible for the metabolism and elimination of many drugs, so patients taking it are likely to experience a reduction in blood levels of drugs they are taking for other purposes, such as cancer chemotherapeutic drugs, protease inhibitors for HIV and hormonal contraceptives.

The scientific field of activity associated with drug safety is increasingly government-regulated, and is of major concern for the public, as well as to drug manufacturers. The distinction between adverse and nonadverse effects is a major undertaking when a new drug is developed and tested before marketing it. This is done in toxicity studies to determine the nonadverse effect level (NOAEL). These studies are used to define the dosage to be used in human testing (phase I), as well as to calculate the maximum admissible daily intake. Imperfections in clinical trials, such as insufficient number of patients or short duration, sometimes lead to public health disasters, such as those of fenfluramine (the so-called fen-phen episode), thalidomide and, more recently, of cerivastatin (Baycol, Lipobay) and rofecoxib (Vioxx), where drastic adverse effects were observed, such as teratogenesis, pulmonary hypertension, stroke, heart disease, neuropathy, and a significant number of deaths, causing the forced or voluntary withdrawal of the drug from the market.

Most drugs have a large list of nonsevere or mild adverse effects which do not rule out continued usage. These effects, which have a widely variable incidence according to individual sensitivity, include nausea, dizziness, diarrhea, malaise, vomiting, headache, dermatitis, dry mouth, etc. These can be considered a form of pseudo-allergic reaction, as not all users experience these effects; many users experience none at all.

Drugs contain side effects which is the reason why commercials or advertisements put many disclaimers about the unwanted symptoms after taking the drug(s) [9].

Drug interaction

A **drug interaction** is a situation in which a substance (usually another drug) affects the activity of a drug when both are administered together. This action can be sinergistic (when the drug's effect is increased) or antagonistic (when the drug's effect is decreased) or a new effect can be produced that neither produces on its own. Typically, interactions between drugs come to mind (drug-drug interaction). However, interactions may also exist between drugs and foods (drug-food interactions), as well as drugs and medicinal plants or herbs (drug-plant interactions). People taking antidepressant drugs such as monoamine oxidase inhibitors should not take food containing tyramine as hypertensive crisis may occur (an example of a drug-food interaction). These interactions may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances.

It is therefore easy to see the importance of these pharmacological interactions in the practice of medicine. If a patient is taking two drugs and one of them increases the effect of the other it is possible that an overdose may occur. The interaction of the two drugs may also increase the risk that side effects will occur. On the other hand, if the action of a drug is reduced it may cease to have any therapeutic use because of under dosage. Notwithstanding the above, on occasion these interactions may be sought in order to obtain an improved therapeutic effect. Examples of this include the use of codeine with paracetamol to increase its analgesic effect. Or the combination of clavulanic acid with amoxicillin in order to overcome bacterial resistance to the antibiotic. It should also be remembered that there are interactions that, from a theoretical standpoint, may occur but which in clinical practice have no important repercussions.

The pharmaceutical interactions that are of special interest to the practice of medicine are primarily those that have negative effects for an organism. The risk that a pharmacological interaction will appear increases as a function of the number of drugs administered to a patient at the same time.

It is possible that an interaction will occur between a drug and another substance present in the organism (ie foodss or alcohol). Or in certain specific situations a drug may even react with itself, such as occurs with dehydration. In other situations the interaction does not involve any effect on the drug. In certain cases, the presence of a drug in an individual's blood may affect certain types of laboratory analysis.

It is also possible for interactions to occur outside an organism before administration of the drugs has taken place. This can occur when two drugs are mixed, fro example, in a saline solution prior to intravenous injection. Some classic examples of this type of interaction include that Thiopentone and Suxamethonium should not be placed in the same syringe and same is true for Benzylpenicillin and Heparin. These situations will all be discussed under the same heading due to their conceptual similarity.

Drug interactions may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion (ADME) of a drug. Alternatively, drug interactions may be the result of the pharmacodynamic properties of the drug, e.g. the co-administration of a receptor antagonist and an agonist for the same receptor.

Synergy and antagonism

When the interaction causes an increase in the effects of one or both of the drugs the interaction is called a synergistic effect . An "additive synergy" occurs when the final effect is equal to the sum of the effects of the two drugs (Although some authors argue that this is not true synergy). When the final effect is much greater than the sum of the two effects this is called enhanced synergy. This concept is recognized by the majority of authors, although other authors only refer to synergy when there is an enhanced effect. These authors use the term "additive effect" for additive synergy and they reserve use of the term "synergistic effect" for enhanced synergy. The opposite effect to synergy is termed antagonism. Two drugs are antagonistic when their interaction causes a decrease in the effects of one or both of the drugs.

Both synergy and antagonism can both occur during different phases of the interaction of a drug with an organism, with each effect having a different name. For example, when the synergy occurs at a cellular receptor level this is termed agonism, and the substances involved are termed agonists. On the other hand, in the case of antagonism the substances involved are known as inverse agonists. The different responses of a receptor to the action of a drug has resulted in a number of classifications, which use terms such as "partial agonist", "competitive agonist" etc. Concepts which have a fundamental application in the pharmacodynamics of these interactions. The proliferation of existing classifications at this level, along with the fact that the exact reaction mechanisms for many drugs are not well understood means that it is almost impossible to offer a clear classification for these concepts. It is even likely that many authors would misapply any given classification.

Drug interactions

These chemical reactions are also known as pharmacological incompatibilities. The reactions occur when two or more drugs are mixed outside the body of the organism for the purpose of joint administration. Usually the interaction is antagonistic and it almost always affects both drugs. Examples of these types of interactions include the mixing of penicillins and aminoglycosides in the same serum bottle, which causes the formation of an insoluble precipitate , or the mixing of ciprofloxacin with furosemide. The interaction of some drugs with the transport medium can also be included here. This means that certain drugs cannot be administered in plastic bottles because they bind with the bottle's walls, reducing the drug's concentration in solution.

Many authors do not consider them to be interactions in the strictest sense of the word. An example is the database of the General Council of Official Pharmacists Colleges of Spain, which does not include them among the 90,000 registered interactions.

Pharmacodynamic interactions

The change in an organism's response on administration of a drug is an important factor in pharmacodynamic interactions. These changes are extraordinarily difficult to classify given the wide variety of modes of action that exist and the fact that many drugs can cause their effect through a number of different mechanisms. This wide diversity also means that, in all but the most obvious cases, it is important to investigate and understand these mechanisms. The well-founded suspicion exists that there are more unknown interactions that known ones [10].

Pharmacodynamic interactions can occur on:

Pharmacological receptors: Receptor interactions are the most easily defined, but they are also the most common. From a pharmacodynamic perspective, two drugs can be considered to be:

Homodynamic, if they act on the same receptor. They, in turn can be:

- *Pure agonists*, if they bind to the main locus of the receptor, causing a similar effect to that of the main drug.
- *Partial agonists* if, on binding to one of the receptor's secondary loci, they have the same effect as the main drug, but with a lower intensity.
- *Antagonists*, if they bind directly to the receptor's main locus but their effect is opposite to that of the main drug. Which, in turn can be:
- *Competitive antagonists*, if they compete with the main drug to bind with the receptor. The amount of antagonist or main drug that binds with the receptor will depend on the concentrations of each one in the plasma.
- *Uncompetitive antagonists*, when the antagonist binds to the receptor irreversibly and is not released until the receptor is saturated. In principle the quantity of antagonist and agonist that binds to the receptor will depend on their concentrations. However, the presence of the antagonist will cause the main drug to be released from the receptor regardless of the main drug's concentration, therefore all the receptors will eventually become occupied by the antagonist.

Heterodynamic competitors, if they act on distinct receptors.

- *Signal transduction mechanisms*: these are molecular processes that commence after the interaction of the drug with the receptor. For example, it is known that

hypoglycaemia (low blood glucose) in an organism produces a release of catecholamines, which trigger compensation mechanisms thereby increasing blood glucose levels. The release of catecholamines also triggers a series of symptoms, which allows the organism to recognise what is happening and which act as a stimulant for preventative action (eating sugars). Should a patient be taking a drug such as insulin, which reduces glycaemia, and also be taking another drug such as certain beta-blockers for heart disease, then the beta-blockers will act to block the adrenaline receptors. This will block the reaction triggered by the catecholamines should a hypoglycaemic episode occur. Therefore, the body will not adopt corrective mechanisms and there will be an increased risk of a serious reaction resulting from the ingestion of both drugs at the same time.

- *Antagonic physiological systems*: Imagine a drug **A** that acts on a certain organ. This effect will increase with increasing concentrations of physiological substance **S** in the organism. Now imagine a drug **B** that acts on another organ, which increases the amount of substance **S**. If both drugs are taken simultaneously it is possible that drug **A** could cause an adverse reaction in the organism as its effect will be indirectly increased by the action of drug **B**. An actual example of this interaction is found in the concomitant use of digoxin and furosemide. The former acts on cardiac fibres and its effect is increased if there are low levels of potassium (K) in blood plasma. Furosemide is a diuretic that lowers arterial tension but which favours the loss of K^+. This could lead to hypopotassaemia (low levels of potassium in the blood), which could increase the toxicity of digoxin.

Pharmacokinetic interactions

Modifications in the effect of a drug are caused by differences in the adsorption, transport, distribution, metabolization or excretion of one or both of the drugs compared with the expected behaviour of each drug when taken individually. These changes are basically modifications in the concentration of the drugs. In this respect two drugs can be homergic if they have the same effect in the organism and heterergic if their effects are different.

Changes in motility

Some drugs, such as the prokinetic agents increase the speed with which a substance passes through the intestines. If a drug is present in the digestive tracts adsorption zone for less time its blood concentration will decrease. The opposite will occur with drugs that decrease intestinal motility [11].

pH: Drugs can be present in either ionised or non-ionised form, depending on their pKa (pH at which the drug reaches equilibrium between its ionised and non-ionised form). The non-ionised forms of the drugs are usually liposoluble, which will facilitate their adsorption by passive diffusion. Obviously increasing the adsorption of a drug will increase its bioavailability and therefore its maximum blood concentration. This fact can be useful when prescribing certain drugs that are not readily adsorbed orally, but it can also be a negative factor as it will cause a reduction in bioavailability in other drugs. In general terms this principle mostly affects acids and weak alkalis, which have a greater tendency for dissociation.

Certain drugs require an acid stomach pH for adsorption. Others require the alkali pH of the intestines. Any modification in the pH could change this adsorption. In the case of the antacids, an increase in pH can inhibit the adsorption of other drugs such as zalcitabine (adsorption can be decreased by 25%), tipranavir (25%) and amprenavir (up to 35%). However, this occurs less often than an increase in pH causes an increase in adsorption. Such as occurs when cimetidine is taken with didanosine. In this case a gap of two to four hours between taking the two drugs is usually sufficient to avoid the interaction.
Drug solubility: The adsorption of some drugs can be drastically reduced if they are administered together with food with a high fat content.

Formation of non-absorbable complexes:

Chelation: The presence of di- or trivalent cations can cause the chelation of certain drugs, making them harder to adsorb. This interaction frequently occurs between drugs such as tetracycline or the fluoroquinolones and dairy products (due to the presence of Ca^{++}).

Binding with proteins. Some drugs such as sucralfate binds to proteins, especially if they have a high bioavailability. For this reason its administration is contraindicated in enteral feeding.

Finally, another possibility is that the drug is retained in the intestinal lumen forming large complexes that impede its adsorption. This can occur with cholestyramine if it is associated with sulfamethoxazol, thyroxine, warfarin or digoxin.

Acting on the P-glycoprotein of the enterocytes: This appears to be one of the mechanisms promoted by the consumption of grapefruit juice in increasing the bioavailability of various drugs, regardless of its demonstrated inhibitory activity on first pass metabolism.

Transport and distribution interactions

The main interaction mechanism is competition for plasma protein transport. In these cases the drug that arrives first binds with the plasma protein, leaving the other drug dissolved in the plasma, which modifies its concentration. The organism has mechanisms to counteract

these situations (by, for example, increasing plasma clearance), which means that they are not usually clinically relevant. However, these situations should be taken into account if there other associated problems are present such as when the method of excretion is affected.

Metabolism interactions

Many drug interactions are due to alterations in drug metabolism. Further, human drug-metabolizing enzymes are typically activated through the engagement of nuclear receptors. One notable system involved in metabolic drug interactions is the enzyme system comprising the cytochrome P450 oxidases [12].

CYP450

Cytochrome P450 is a very large family of haemoproteins that are characterized by their enzymatic activity and their role in the metabolism of a large number of drugs. Of the various families that are present in human beings the most interesting in this respect are the 1, 2 and 3, and the most important enzymes are CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.[19] The majority of the enzymes are also involved in the metabolism of endogenous substances, such as steroids or sex hormones, which is also important should there be interference with these substances. As a result of these interactions the function of the enzymes can either be stimulated (enzyme induction) or inhibited (enzyme inhibition).

Enzymatic inhibition

If drug A is metabolized by a cytochrome P450 enzyme and drug B inhibits or decreases the enzyme's activity, then drug A will remain with high levels in the plasma for longer as its inactivation is slower. As a result, enzymatic inhibition will cause an increase in the drug's effect. This can cause a wide range of adverse reactions.
It is possible that this can occasionally lead to a paradoxical situation, where the enzymatic inhibition causes a decrease in the drug's effect: If the metabolism of drug A gives rise to product A_2, which actually produces the effect of the drug. If the metabolism of drug A is inhibited by drug B the concentration of A_2 that is present in the blood will decrease, as will the final effect of the drug [13].

Enzymatic induction

If drug A is metabolized by a cytochrome P450 enzyme and drug B induces or increases the enzyme's activity, then blood plasma concentrations of drug A will quickly fall as its inactivation will take place more rapidly. As a result, enzymatic induction will cause a decrease in the drug's effect.

As in the previous case it is possible to find paradoxical situations where an active metabolite causes the drug's effect. In this case the increase in active metabolite A_2 (following the previous example) produces an increase in the drug's effect.
It can often occur that a patient is taking two drugs that are enzymatic inductors, one inductor and the other inhibitor or both inhibitors, which greatly complicates the control of an individual's medication and the avoidance of possible adverse reactions.

New Chemical Entity (NCE) development

Pre-clinical. New Chemical Entities (NCEs)(also known as New Molecular Entities [NMEs]) are compounds which emerge from the process of drug discovery. These will have promising activity against a particular biological target thought to be important in disease; however, little will be known about the safety, toxicity, pharmacokinetics and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials. A further major objective of drug development is to make a recommendation of the dose and schedule to be used the first time an NCE is used in a human clinical trial ("first-in-man" [FIM] or First Human Dose [FHD]).

In addition, drug development is required to establish the physicochemical properties of the NCE: its chemical makeup, stability, solubility. The process by which the chemical is made will be optimized so that from being made at the bench on a milligram scale by a synthetic chemist, it can be manufactured on the kilogram and then on the ton scale. It will be further examined for its suitability to be made into capsules, tablets, aeresol, intramuscular injectable, subcuteneous injectable, or intravenous formulations. Together these processes are known in preclinical development as Chemistry, Manufacturing and Control (CMC) [14].

Many aspects of drug development are focused on satisfying the regulatory requirements of drug licensing authorities. These generally constitute a number of tests designed to determine the major toxicities of a novel compound prior to first use in man. It is a legal requirement that an assessment of major organ toxicity be performed (effects on the heart and lungs, brain, kidney, liver and digestive system), as well as effects on other parts of the body that might be affected by the drug (e.g. the skin if the new drug is to be delivered through the skin). While, increasingly, these tests can be made using in vitro methods (e.g. with isolated cells), many tests can only be made by using experimental animals, since it is only in an intact organism that the complex interplay of metabolism and drug exposure on toxicity can be examined.

The information gathered from this pre-clinical testing, as well as information on CMC, and is submitted to regulatory authorities (in the US, to the FDA), as an

Investigational New Drug application or IND. If the IND is approved, development moves to the clinical phase.

Clinical phase

Clinical trials involves three steps: Phase I trials, usually in healthy patients, determine safety and dosing; Phase II trials are used to get an initial reading of efficacy and further explore safety in small numbers of sick patients; Phase III trials a large, pivotal trials to determine safety and efficacy in sufficiently large numbers of patients.

The process of drug development does not stop once an NCE begins human clinical trials. In addition to the tests required to move a novel drug into the clinic for the first time it is also important to ensure that long-term or chronic toxicities are determined, as well as effects on systems not previously monitored (fertility, reproduction, immune system, etc.). The compound will also be tested for its capability to cause cancer (carcinogenicity testing) [15].

If a compound emerges from these tests with an acceptable toxicity and safety profile, and it can further be demonstrated to have the desired effect in clinical trials, then it can be submitted for marketing approval in the various countries where it will be sold. In the US, this process is called a New Drug Application or NDA. Most NCEs, however, fail during drug development, either because they have some unacceptable toxicity, or because they simply do not work in clinical trials.

Clinical trials are a set of procedures in medical research and drug development that are conducted to allow safety (or more specifically, information about adverse drug reactions and adverse effects of other treatments) and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols). These trials can take place only after satisfactory information has been gathered on the quality of the non-clinical safety, and Health Authority/Ethics Committee approval is granted in the country where the trial is taking place [16].

Fig 1. Dose response curve

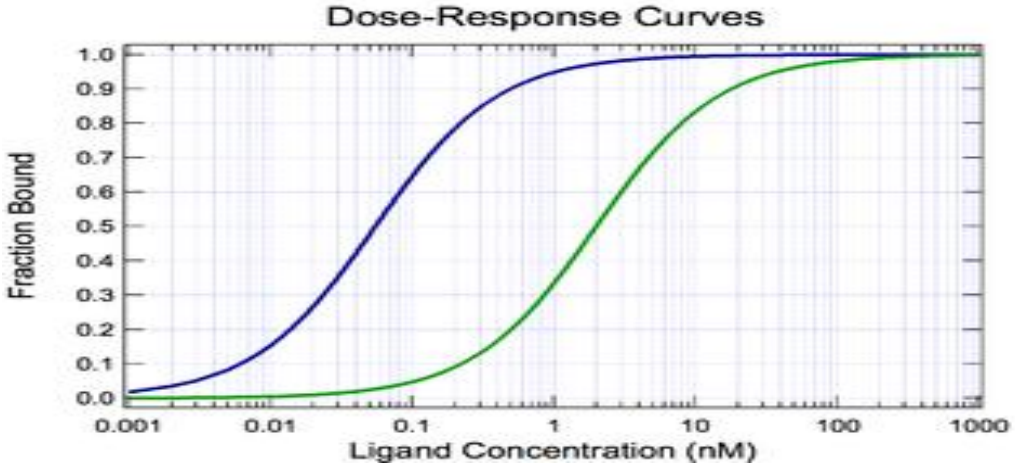


Fig 2. Plasma drug concentration vs time after an IV dose

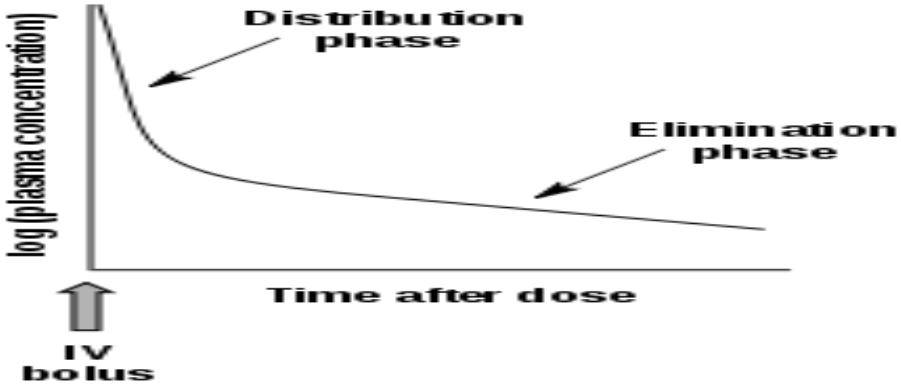
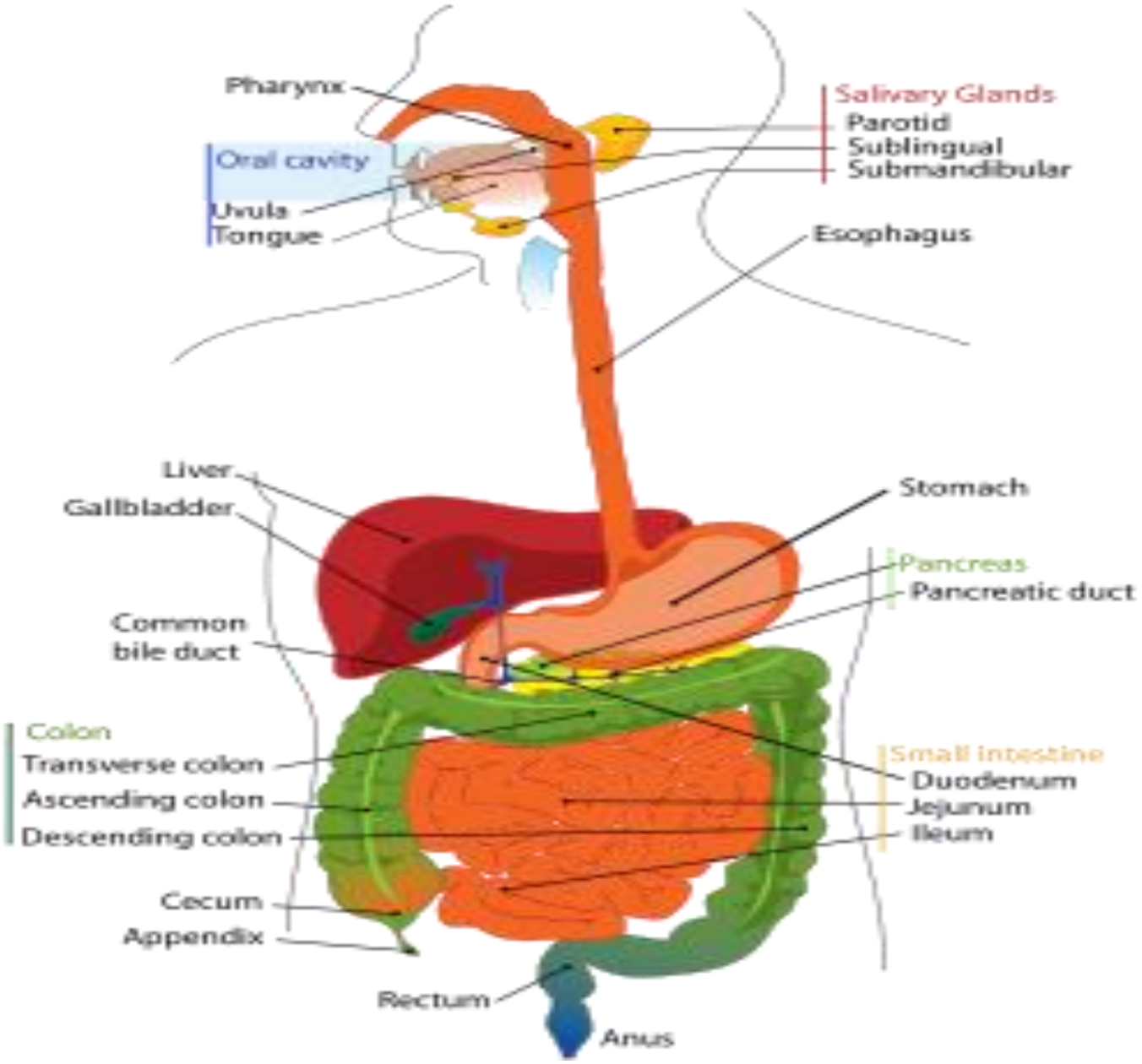


Fig 3. Lumen of the digestive tract Changes in the lumen of the digestive tract



CONCLUSION

Depending on the type of product and the stage of its development, investigators enroll healthy volunteers and/or patients into small pilot studies initially, followed by larger scale studies in patients that often compare the new product with the currently prescribed treatment. As positive safety and efficacy data are gathered, the number of patients is typically increased. Clinical trials can vary in size from a single center in one country to multicenter trials in multiple countries. Due to the sizable cost a full series of clinical trials may incur, the burden of paying for all the necessary people and services is usually borne by the sponsor who may be a governmental organization, a pharmaceutical, or biotechnology company. Since the diversity of roles may exceed resources of the sponsor, often a clinical trial is managed by an outsourced partner such as a contract research organization or a clinical trials unit in the academic sector.

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