

**PEOPLE'S DEMOCRATIC REPUBLIC OF ALGERIA
MINISTRY OF HIGHER EDUCATION AND SCIENTIFIC RESEARCH**

BADJI Mokhtar Annaba University

Faculty of Sciences

Department of Chemistry



Pharmacotoxicology

Field of Material Sciences

For third year L₃ students

Pharmaceutical chemistry specialty

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FOREWORD

Compliant with the official LMD programs, this pharmacotoxicology course handout is aimed at third-year higher education students in the field of Material Sciences specializing in pharmaceutical chemistry. It is designed to clarify the main concepts related to pharmacology ; toxicology and to develop the bases necessary for their application in the pharmaceutical field. Pharmacotoxicology encompasses pharmacology and toxicology.

Pharmacology is a science that studies the biological interactions of drugs, their dosage and their therapeutic indications. According to the WHO, medicine is any substance or product used or intended to be used to modify or study a physiological system or a pathological state in the interest of the subject to whom it is administered.

The program consists of five main parts:

The first part is devoted to the study of the pharmacology in general.

The second part concerns pharmacokinetics and pharmacodynamics of drugs. The objective of this chapter is to understand the mechanism of action of drugs and to explain their therapeutic effects. In particular, the notions of therapeutic target, pharmacodynamics and the basic concepts of pharmacokinetics will be addressed.

The third part concerns toxicology, it studies poisons, their detection and their effects. A poison is a toxic substance, when it enters the body, by any route and whatever its dose causes disorders of one or more vital functions which can lead to death.

Fourth part highlights drug poisoning.

The last chapter devoted to non-drug poisonings.

SEMESTRE 5

Unité d'Enseignement	VHS	V.H hebdomadaire				Coeff	Crédits	Mode d'évaluation	
		C	TD	TP	Travail Personnel			Continu	Examen
UE fondamentales 5						12	20		
Méthodes spectroscopiques d'analyses	67h30	3h	1h30			3	5	X	x
Chimie organique approfondie I	67h30	3h	1h30			3	5	X	X
Chimie organique pharmaceutique	67h30	3h	1h30			3	5	X	X
Méthodes d'analyses électrochimiques	67h30	3h	1h30			3	5	X	X
UE méthodologie 5						4	6		
Pharmacologie-Toxicologie	28h30	1H30		0,4h		2	3	X	X
TP Synthèse d'intermédiaires organiques pour les molécules bioactives	22h30			1h30		2	3		
TP Electrochimie	22h30			1h30		2	3		
UE découverte 5						1,5	3		
Initiation à la connaissance du médicament	22h30	1h30				1,5	3	X	X
UE transversales 5						1,5	3		
Langue anglaise 5	22h30	1h30				0,5	1	X	X
Total Semestre 5	366	247,5	90	51		15	30		

UEM5

PHARMACO- TOXICOLOGY

Medicinal toxicants (concepts of pharmacotoxicology, definition of medicinal toxicants, benzodiazepines), non-drug toxicants (metals, insecticides, herbicides, hydrocarbons, etc.).

Module content

Chapter I: Pharmacology

- Definition of Pharmacology
- The fields of pharmacology
- Definition of medicine
- Name of medicines
- Classification of drugs in different tables or lists
- Characteristics of a drug
- Medicine Categories

Chapter II: Pharmacokinetics and Pharmacodynamics

-Pharmacokinetics

- ☐ Absorption.
- ☐ Distribution.
- ☐ Metabolism.
- ☐ Elimination.

-Pharmacodynamics

- Ligand-receptors
- Agonist-Antagonist
- Tolerance, Desensitization, Hypersensitization and dose-effect relationship
- Drugs interactions

Chapter III: Toxicology

- General concepts in toxicology
- Classification of toxicants
- Dose-response relationship
- Different types of toxicity
- Difference between exposure and effect
- Areas of study of toxicology
- Drug toxicology
- Dose and modulation of toxic effects
- The fight against intoxication

Chapter IV: Drug poisonings

- Poisoning by Benzodiazepines
- Poisoning by medicinal carbamates
- Poisoning by tricyclic antidepressants
- Paracetamol poisoning
- Barbiturate poisoning
- Opiate poisoning (Morphine, heroin, codeine)
- Cocaine poisoning

Chapter V : non-drug poisonings

- Carbon monoxide

- Benzene poisoning
- Heavy metals
- Organophosphates
- Organochlorines

Abbreviation

WHO: World Health Organization

INN: International Common Name

GH: Growth Hormone

IUPAC: International Union of Pure and Applied Chemistry

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

AMM: Marketing Authorization

Mg: Milligram

Kg: Killogram

M: Meter

P: Pressure

PD: Pharmacodynamic

Pka: Acid dissociation constant

pH : Hydrogen Potential

min: Minute

l: Liter

HDL: High Density Lipoprotein

LDL : Low Density Lipoproteins

VLDL: Very Low Density Lipoproteins

Ka: Association constant

α : Alpha

NADP: Nicotinamide Adenine Dinucleotide Phosphate

Cl: Clearance

ml: Milliliter

h: Hour

C: Concentration

Q: Blood flow

E: The extraction coefficient

MW: Molecular Weight

Rex: Excretion ratio

Pb: Plomb

Hg: Mercury

Fe: Iron

ED50: Effective Dose 50

LD50: Lethal Dose 50

g: Gram

CO: Carbon monoxide

HbCO: Carboxyhemoglobin

SO: Organic Solvent

µm: Micrometer

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Chapter I: Pharmacology

Ancient civilizations used a mixture of magic, religion and drugs to treat illnesses and often attributed magical powers to these drugs.

In ancient times, most medicines came from plants and animal fragments or fluids.

Knowledge of drugs has grown alongside knowledge of body functions (anatomy, physiology, biochemistry) and chemistry.

Modern drugs are developed in association by university and industrial structures.

I.1. Definition of Pharmacology

The word “pharmacology” comes from the Greek word *pharmakon* which designates medicine, but also poison and *logos* which means science. It is the science of the effects and fate of medications in the body. It differs from the pharmacy which manufactures and dispenses (gives, distributes) the medicine.

I.2. The fields of pharmacology

Pharmacology covers an extremely broad field, it includes apart from pharmacokinetics, pharmacodynamics, pharmacovigilance and drug dependence, the study of drugs in animals (experimental pharmacology) or in humans (clinical pharmacology), pharmacoepidemiology, pharmacoeconomics and pharmacosociology and many other fields.

1.2. 1. Terminology

❖ Pharmacogenetics

Study of the influences of ethnicity on the pharmacokinetic and pharmacodynamic properties of drugs.

Exp: acetylation polymorphism (N acetyl transferase) Isoniazid (anti-tuberculosis): slow/fast acetylators (depending on race: fast white; slow black).

❖ Pharmacoeconomics

The study of the price of medicines and take into consideration: - Financial cost of the medicine for the patient/Financial cost of the medicine for the laboratory.

❖ **Pharmacodynamics**

It describes what the medicine does to the body: it is the detailed study of how medicines act (the receptor/active substance interaction). This response is a component of the desired therapeutic effect.

❖ **Pharmaco-epidemiology**

Characterization of drug use in different populations or social groups.

❖ **Pharmacokinetics**

Aims to study the fate of an active substance contained in a drug in the body. It includes four phases, taking place simultaneously.

❖ **Pharmacovigilance**

It is the study of methods for detecting and preventing adverse effects.

***Adverse reaction:** a harmful and unwanted reaction occurring at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or modification of physiological function, or resulting from misuse of the drug or product.

❖ **Chemical Pharmacy**

Studies preparation, testing and dosage.

❖ **Pharmacotoxicology**

Studies the physiological action of drugs on the body. It seeks to establish the relationship between,

*the body's sensitivity to the drug; tolerance and intolerance.

*the influence of chemical constitution on medicinal activity...

*drug combinations; synergy and antagonism.

❖ **Galenic Pharmacy**

Studies methods of drug design.

I.3. Definition of medicine

A medicine is any substance or composition presented as having preventive or curative properties with regard to human or animal diseases. It also includes any product that can be

administered to humans or animals with a view to establishing a medical diagnosis or restoring, correcting or modifying their organic functions.

Medicines = active ingredients + excipients + pharmaceutical form (**Figure 1**).

***Active ingredients**

Carrying out pharmacological activity, are designated by a one-word abbreviated name made official by the WHO, the international non proprietary name or INN.

***Excipients**

Ensure the preservation of the medicine, give it a volume and a presentation usable by the patient and allow its identification.

Important role in the speed at which the active ingredient is made available to the body. **Inactive** in terms of their therapeutic benefit, they can however cause **harmful effects**.

1.3.1. Functions of the drug

A. Therapeutic functions

- ✓ Preventive: - individual: vaccination – malaria.
- collective: collective chemoprophylaxis of meningitis.
- ✓ Curative: -etiology: treats the cause (origin)
 - Substitutive: by completing the lack
 - symptomatic: treating the symptom (without eradicating the cause)

B. Diagnostic functions: functional exploration: imaging and medical radiology (exp: iodinated contrast product).

I.4. Origin of drugs

Medicines can be obtained from a wide variety of sources.

- **Plant origin:** this is the oldest source, but which remains relevant; we can cite alkaloids (quinine, morphine, etc.), glycosides (digoxin, digitoxin, etc.), gums (laxative mucilages, gum arabic).

- **Animal origin:** human blood extracts (whole blood, plasma, cells), hormones (gonadotropins, etc.), enzymes (trypsin, chymotrypsin, etc.), heparin.

- **Synthetic origin:** most of the drugs currently marketed are of synthetic origin, obtained by total synthesis or semisynthesis (certain penicillins: M and A, etc.), sulfonamides (antibiotics: Flammazine and antidiabetics: GLIBENESE), barbiturates (GARDINAL).
- **Microbial origin:** antibiotics (penicillins: penicillin G produced by *Penicillium notatum*, streptomycin) and certain anticancer drugs (doxorubicin, bleomycin, streptozotocin, etc.)
- **Biogenic origin:** “genetic engineering” methods are the latest, they allow living cells – prokaryotes or eukaryotes – to produce natural polypeptide substances presenting all the characteristics of their human model: “humanized insulin: Insuman®”, growth hormone (GH), different types of interferons (α , β , γ), hematopoietic growth factors (erythropoietin), angiogenic inhibitor antibodies (Bivacizumab or AVASTIN®) for treatment of breast cancer (authorized in February 2004).

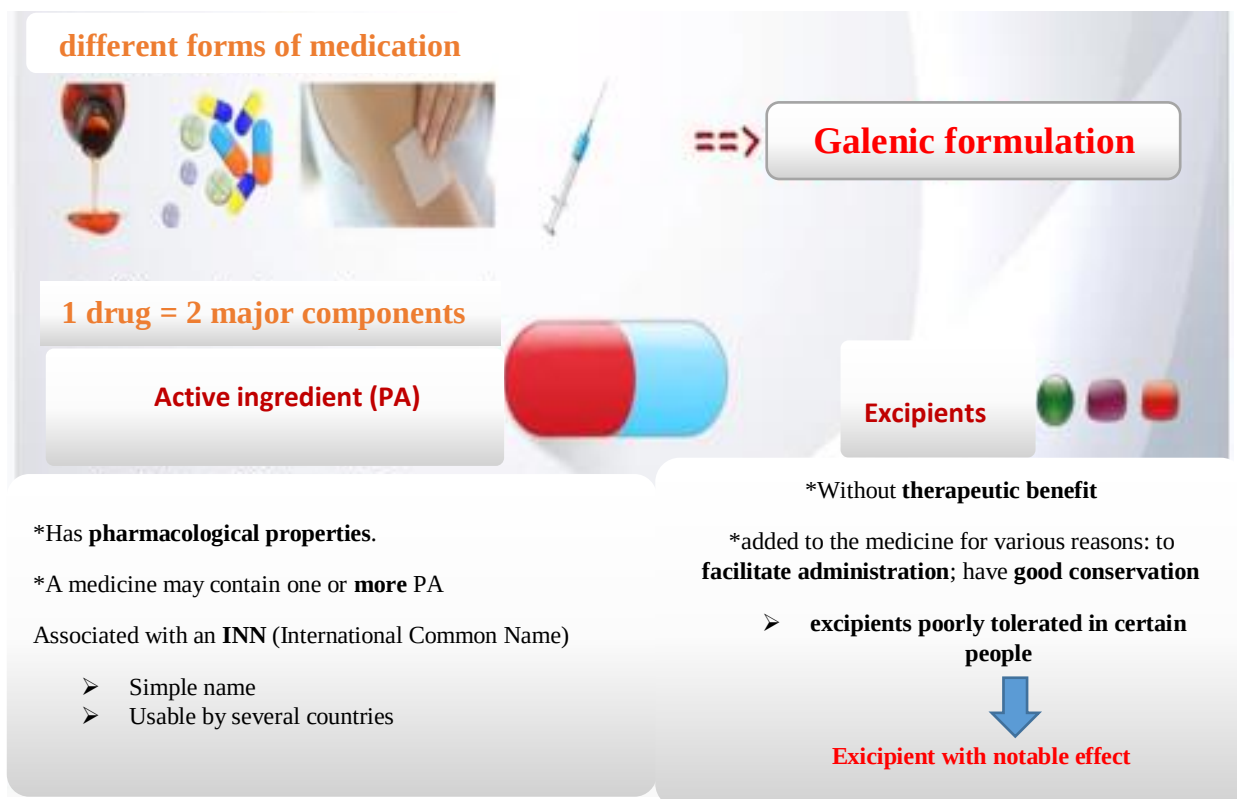


Figure.1. Some basics about medications [1].

1.5. Name of medicines

Each medicine has a name; We can distinguish:

1.5.1. The scientific or chemical name: meeting the international nomenclature but often too complicated to be used in daily practice.

Ex: Acetyl salicylic acid.

1.5.2. The international non-proprietary name (INN): giving each active ingredient a simple name that can be used in all countries (WHO proposal)

Ex: Aspirin.

1.5.3. The commercial or special name: (Pharmaceutical specialty), this is the brand name registered by the manufacturer. They are generally written in capital letters.

Ex: CATALGINE®.

Each drug has at least three names:

A. chemical name

This chemical name is developed using very strict nomenclature rules decreed by IUPAC (international union of pure and applied chemistry): it is the literal translation of the structural formula: phenylethylpropylpropanediol.

B. An international nonproprietary name or “INN”

This is the name recommended by the “WHO”, making it possible to exclude any commercial influence for the choice of name. Thus, DCIs are generally built from a key segment, which makes it possible to identify the main activity of the product simply by reading or hearing.

C. The commercial or special name

(Pharmaceutical specialty), this is the brand name registered by the manufacturer. They are generally written in capital letters.

Ex: CATALGINE®.

1.6. Classification of drugs in different tables or lists

***FREE SALE:** “non-dangerous drugs” (aspirin, paracetamol, etc.)

***TABLE C (list I):** toxic drug at high doses (laxatives, antacids, etc.)

***TABLE A (list II):** low dose toxic medication (antibiotics, cardiotonics, etc.)

***TABLE B** (list of narcotics): narcotics, addictive drugs (morphine, heroin, etc.)

EXEMPTION: medicine containing a quantity less than a limit set by decree and sold freely (codeine syrup).

1.7.Characteristics of a drug

The medicine is a finished industrial product (not a substance)

A. The name: present

- **Trade name or NC:** the name designated by the laboratory manufacturing this medicine. Ex: Doliprane.

- **International nonproprietary name or INN:** the chemical name of the active ingredient (active ingredient is the substance responsible for the pharmacological effect). Ex: Paracetamol. It is found under the N.C.

B. Dosage: the content (quantity) of the active ingredient contained in a basic unit. Ex: a tablet contains 25mg of PA, for the syrup a 5 ml scoop contains 10mg of active ingredient.

NB: dose $\neq$ dosage, the dose is the quantity given to a patient.

C. Pharmaceutical form (galenic form): determines the route of administration and the method of use.

-Solid form: tablet, capsule.

-Liquid form: syrup, drops, oral or injectable suspensions.

-Pasty form: gel ointment, cream, suppositories.

1.8. Classification of drugs

There are several ways to classify drugs:

A. Therapeutic Classification

It is a group of drugs that share the same indication (an indication is the pathology treated by this drug) and therefore the name of the pathology must be part of the name of this class.

Ex: antiallergics, antidiabetics, anti-infectives, antiepileptic antidepressants anticancer.

B. Pharmacological Classification

It is a group of drugs that share the same pharmacological effect (the pharmacological effect is the modification of a pathophysiological state caused by a drug). Ex: anti-inflammatories, anticoagulants, analgesics, antibiotics, hypoglycemics.

C. Chemical Classification

It is a group of drugs that share the same chemical structure. Ex: sulfonamides, corticosteroids have the same steroid structure.

NB: we can combine 2 Classification criteria: Pharmaco-chemical:

Ex: Non-steroidal anti-inflammatory drugs (NSAIDs).

1.9. Medicine Categories

There are three types of drugs

***The compounded medication:** Prepared on request by the pharmacist according to the composition described by the doctor. It is intended for a single patient (example: dermatological preparation).

***The medicinal product:** Without AMM, prepared in advance either by the pharmacist at the pharmacy or industrially. Examples; Iodized alcohol, Eosin, salicylated vaseline...

***Specialty medicine:** Subject to the MA procedure (example: Antibiotics, vaccines, etc.).

Pharmaceutical Specialties = any medicine prepared in advance, presented in particular packaging and characterized by a special name = International Nonproprietary Name = INN = scientific name (NON-commercial name) of the molecule = active substance. INNs are established by the World Health Organization (WHO) which creates them, with key segments, according to their therapeutic class, taking care to avoid confusion.

The generic drug

The first drug marketed for an INN is called “princeps”

The originator is protected by a patent (a document which establishes the intellectual property of the laboratory to this drug for a period of approximately 20 years during which it is prohibited

to produce a generic drug) because of the significant cost and time necessary for the development of 'a new drug because the price of the generic is lower than that of the original drug.

The generic specialty is defined as: “one which has the same composition, qualitative and quantitative in active principle, the same pharmaceutical form, and whose bioequivalence with the reference specialty is demonstrated by appropriate bioavailability studies...” Article L.601.6 of the public health code.

The name of the generics is:

- Either the INN followed by the name of the laboratory.
- Either a fancy name which must then be followed by “Gé.

At the end of the patent, generic medicines can be marketed with the following criteria:

*same INN.

* same dosage.

*same shape.

*the generic must be recognized as organic equivalent to the originator.

Concept of dosage

The dosage is expressed in quantity of active ingredient and not by the weight of the medication. In fact, it is the quantity of active ingredient per dose per day to obtain the optimal therapeutic effect:

mg/kg/day or in mg/m^2

where $s = 0.1 \times 0.683$

I.10. General notions on pharmaco-toxicology

Pharmacology is a crossroads discipline that touches on pharmacy, chemistry, biology, genetics, pathology, therapeutics and many other sciences. It itself is subdivided into multiple specialties: Pharmacokinetics, pharmacodynamics (PD), clinical pharmacology (drugs and humans), therapeutic trials (testing of drugs in humans), drug dependence.

Toxicology has long been recognized as the science of poisons. It is a collection of knowledge concerning poisons, their effects on the body, the means of detecting them and the therapeutic processes intended to combat them (**Figures 2 and 3**).

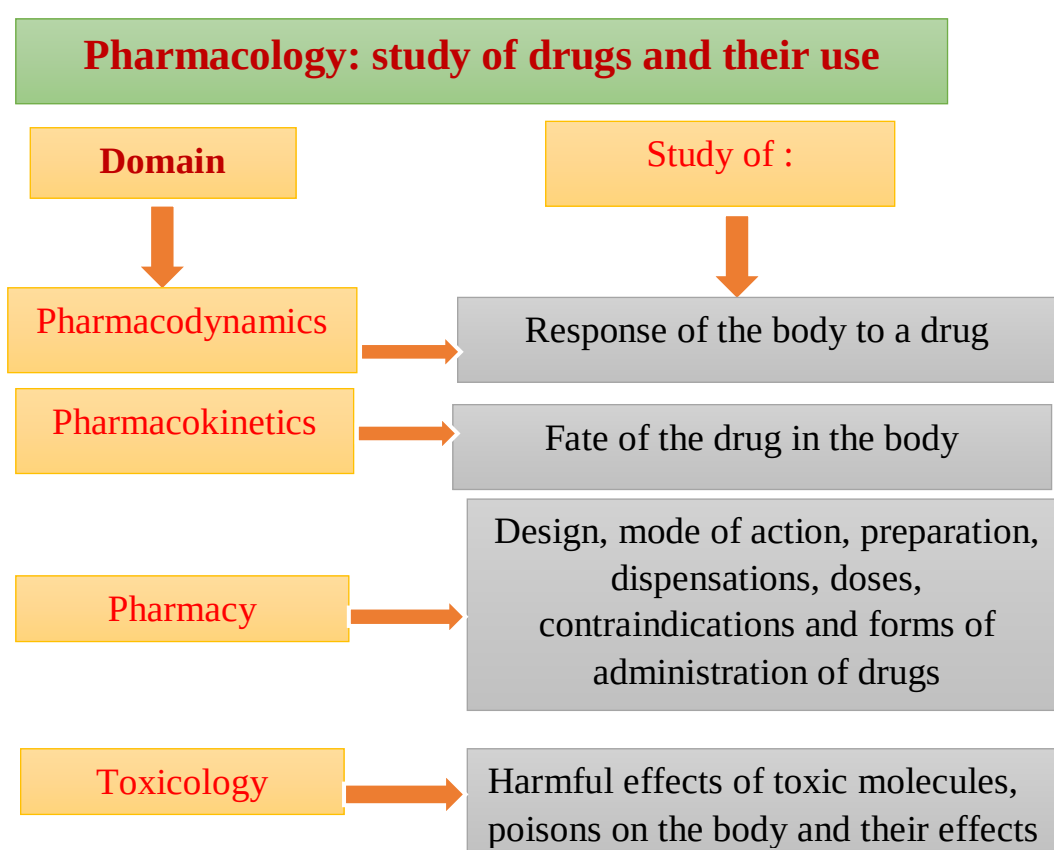


Figure.2. Some definitions [1]

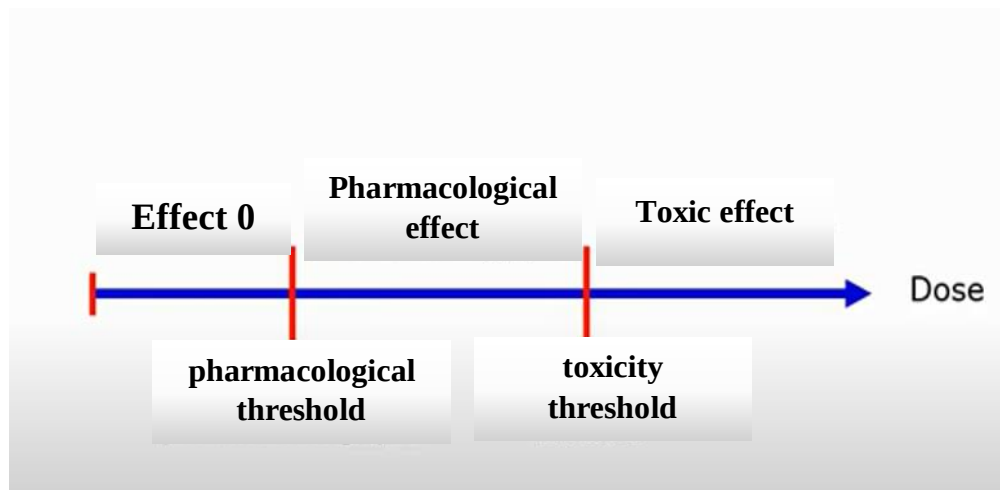


Figure.3. Pharmacology-toxicology relationship [1].

Chapter II: Pharmacokinetics and Pharmacodynamics

II.1. Pharmacokinetics

Aims to study the fate of an active substance contained in a drug in the body. It includes four phases, taking place simultaneously:

- ☐ Absorption.
- ☐ Distribution.
- ☐ Metabolism.
- ☐ Elimination.

Note: Determining the pharmacokinetic parameters of an active substance provides information, which makes it possible to choose the routes of administration and the dosage form, and to adapt the dosages for its future use.

II.1.A. Absorption

First step in pharmacokinetics

* Pass the active ingredient from the site of administration into the general circulation (or systemic circulation).

* More or less rapid depending on the route of administration of the drug.

- **Enteral route:** passage through the digestive tract before entering the general circulation. (Stomach > Liver > Degradation of PA by the digestive ducts and the liver (certain quantity of inactive PA) “Hepatic first pass effect (EPPH)”

- **Parenteral route:** direct passage into the blood (general circulation) example: intravenous route.

• The physicochemical properties involved in the absorption of drugs

*The ionization state

The active ingredients of drugs generally have either a weak acid or base character low, Example: Aspirin $pK_a = 3.5$; Paracetamol $pK_a = 9$

They will therefore be likely to ionize depending on the pH of the environment where they are located, and their pKa, according to the Henderson-Hasselbalch equation.

***Fat solubility**

the more lipid soluble the drug, the more PA passes a lipid membrane.

***Water solubility**

Substances that are poorly water-soluble are poorly resorbed at the digestive level because the quantity is found in solution is very limited, therefore water solubility is a limiting factor in the dissolution of medicines in the digestive system.

*** Molar mass**

The speed of transfer of a drug is inversely proportional to its molar mass.

The dissolved, non-ionized and sufficiently lipid-soluble active ingredients pass through the biological membranes of the absorption site

- **The mechanisms involved in drug absorption**

The main barrier that the drug encounters is the plasma cell membrane, composed of a lipid bilayer.

a) Passive diffusion

It represents the most important mechanism by which active ingredient molecules pass to across membranes when these molecules are not electrically charged.

*Concerns non-ionized fat-soluble molecules.

*Is done in the direction of the concentration gradient.

*Does not require energy and carriers.

*The physicochemical properties of the drug determine passive diffusion.

b) Facilitated passive diffusion

*The transfer of molecules occurs in the direction of the concentration gradient.

*It is a phenomenon that requires a transporter (a membrane protein).

*It is a saturable and specific phenomenon.

c) Active transportation

* Is done in the opposite direction of the concentration gradient.

*Requires a transporter (a membrane protein), and energy.

*Active transport is specific and saturable.

d) Filtration

Passage of molecules through the pores of the plasma membranes.

e) Pinocytosis

The absorption of drugs according to the different routes of administration:

1-absorption of oral medications:

1.a. Anatomical elements involved in the digestive absorption of drugs

The passage of active ingredients through the gastrointestinal mucosa involves all transmembrane transport mechanisms: passive diffusion; active transportation; easy distribution; filtration and pinocytosis (**Table 1**).

Anatomical elements	Physiological characteristics	PH	Vascularization
The stomach	- Made up of a thick membrane with a small absorption surface (1 m ²) - Under normal conditions, gastric emptying is rapid and the role of the stomach in the absorption of medicine is modest.	1-3	Weak (blood flow = 0.2 l/min)
Duodenum	- Significant exchange surface - Presence of bile favoring the dissolution of active substances	4-5	Important

The intestine	The membrane is thin with a very large surface area absorbent (microvilli) (200 m²). - The small intestine is therefore the most important site for drug absorption	5-8	Very Important (blood flow = 1 l/min)
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Table.1. Anatomical elements involved in the digestive absorption of drugs [2].

1.b. Diffusion of drugs by pH effect

Only the non-ionized and lipid-soluble fraction crosses the digestive barrier into the blood (pH = 7.4), lipid-protein nature (by passive diffusion).

The pH varies between 1 and 8 in the digestive tract, depending on this pH value, the ratio of forms ionized and non-ionized depends on the pKa of the compound.

For a weak acid

*In an acidic environment: ionization is low, the non-ionized fraction is greater, the drug will pass cell membranes better.

*In basic medium: ionization is important, hence a larger ionized fraction, which will limit the transmembrane passage of this substance.

For a weak base

*In an acidic environment: the ionization will be greater, hence a greater ionized fraction, the drug will have difficulty passing cell membranes.

* In basic medium: ionization is low, the drug will pass membranes well cellular.

N.B: before its absorption a certain quantity of the active ingredient can be metabolized or transformed under the effect of certain intestinal enzymes (Disaccharisadases, Dipeptidases, Enterokinase, Cytochromes) or enzymes of the intestinal flora into transformation products called metabolites “It’s the effect of the first intestinal passage”.

After absorption, the active ingredients reach the portal vein which goes to the liver. At this level, a fraction can be metabolized (= chemically transformed). This phenomenon called “Effect of first hepatic pass” can considerably reduce the quantity of these active ingredients before to achieve blood circulation.

- **Factors modifying the absorption of drugs:**

- a. **The physiological constituents of digestion**

Digestive secretions (acidic stomach pH; intestinal flora, etc.) can cause physicochemical modifications of drug molecules.

- b. **Food**

It is difficult to predict the influence of diet on the digestive absorption of drugs.

Eating a meal causes the following changes:

- *Increased splanchnic blood flow.

- *Decreased gastric emptying (high-fat meal).

- *Increased bile secretion.

- c. **Gastric emptying**

The factors influencing gastric emptying are:

- ❖ Food.

- ❖ Physical exercise.

- ❖ Body position.

- ❖ Drug interactions.

- d. **Splanchnic blood flow**

It directly influences the absorption of lipid-soluble drugs.

- **Drug interactions in pharmacokinetic phases**

It is the consequence of modifications made by one of the associated drugs on the factors limiting the digestive absorption of drugs, namely: dissolution; gastric emptying; And intestinal blood flow.

- **Pathological conditions**

The absorption of drugs can be modified by disturbances in intestinal transit, secretions and the state of the intestinal mucosa (**Table 2**).

The level of disruption	Examples	Result
Digestive secretions	-Absence of factor secretion Intrinsic Decreased absorption of vitamin B12 -Absence of bile secretion	-Decreased absorption of vitamin B12 -Decreased absorption of vitamin K
Intestinal mucous membranes	Villi degeneration intestinal (Crohn's disease)	Decreased absorption of all medications
Intestinal transit	Reduction in contact time of medicine with mucosa intestinal (diarrhea)	Decreased absorption of all medications

Table.2. Pathological conditions [2].

2. Sublingual absorption

The medicine is placed under the tongue, an area bounded by a mucous membrane similar to that of the digestive tract, conditions favorable to drug absorption at this level:

- Thin epithelium.
- PH weakly acidic.
- Rich in vascularization allowing passage through the oral mucosa to the environment blood.

Any medication absorbed this way will prevent:

- The action of the different gastric pH.
- Digestive enzymes.
- Bacterial flora.
- Hepatic metabolism (first hepatic passage).

3. Rectal absorption

- It is done by passive diffusion.
- The lower and middle hemorrhoidal veins lead to the internal iliac veins which flow into the inferior vena cava thus avoiding the first hepatic passage.
- The superior hemorrhoidal veins are connected to the inferior mesenteric vein which brings blood to the portal vein then to the liver.

Note: it is difficult to predict with certainty the proportion of drug administered per route rectal which will avoid the first hepatic passage.

4. Absorption via the pulmonary route

The lungs constitute an excellent organ of absorption by their:

- ✓ Large exchange surface (the number of cells varies between 300 to 400 million).
- ✓ Very high permeability.
- ✓ Very significant vascularization.

Absorption by this route of administration occurs by passive diffusion at the membrane level Alveolar.

5. Parenteral absorption

Absorption of medications is generally rapid by injection of the medication directly.

in the body (with the exception of the intravenous and intra-arterial route). And this while avoiding elimination through the gastrointestinal tract. However, drugs administered directly in the systemic circulation may undergo first-pass elimination through the lungs before being distributed to the rest of the body. We distinguish:

a. Absorption of drugs intramuscularly

Resorption occurs by passive or facilitated diffusion.

The active ingredients are absorbed fairly quickly depending on: their liposolubility and the vascularization and blood flow at the injection site.

b. Subcutaneous absorption

Resorption occurs by passive or facilitated diffusion, the speed of resorption is lower than that by intramuscular route due to the viscosity of the ground substance of the connective tissue (the addition of an enzyme: hyaluronidase which reduces this viscosity).

II.1.B.Distribution

Second stage of pharmacokinetics

*Pass the PA from the general circulation (or systemic circulation) to the target tissues

*Corresponds to the process of distributing the drug throughout tissues and organs.

-Bound form: Binding of **PA reversibly** to plasma proteins; for example, albumin does not allow the diffusion of PA into the tissues.

-Free form: PA can diffuse into tissues; pharmacologically active drug.

FREE FORM = ACTIVE FORM

A. Blood distribution

 **Binding to plasma proteins:** reversible phenomenon depend on the concentration of the binding protein the affinity of the drug for this protein.

Plasma proteins involved in the binding of drugs:

- Albumin.
- α -acid glycoprotein.
- Globulins (α , β , γ).
- Lipoproteins (HDL, LDL, VLDL).

 **Characteristics of plasma drug fixation:**

- Specificity

There are specific binding sites for certain drugs.

- **Affinity:**

Expressed by the affinity or association constant K_a .

- **Number of fixation sites:**

The binding sites on a protein can be restricted or numerous.

- **Fixation percentage:**

Allows drugs to be classified into: strongly fixed, moderately fixed and weakly fixed.

- **Binding of weak acid drugs**

Albumin is the only carrier protein. The affinity is high, against the number of sites is low.

- **Binding of weak base drugs**

Weak base drugs bind to all proteins circulating but with respect to albumin the affinity is low and the number of sites is high.

- **Factors that influence protein binding**

Variation of fixation if:

- Fluctuations in plasma protein concentrations.
- Modification of the conformation of albumin.
- Competition on the same binding site.

- **Link site**

- Weak acid drugs: reduced number of binding sites, affinity larger and saturable fixation.
- Weak base drugs: greater number of binding sites, lower affinity and unsaturable fixation.

- **Age**

- Newborn: Structural modification of albumin + ↑ bilirubin and Fatty acids
- Elderly: Hypoalbuminemia.

- **Pathological factors**

- Liver failure, renal failure, burns: hypoalbuminemia
- Neurosis, psychosis, schizophrenia: Hyper albuminemia.
- Myocardial infarction, Crohn's disease: ↑ α 1-acid glycoprotein.
- Chronic infections: ↑ γ -globuline.
- Hyperthyroidism: ↑ lipoproteins.

- **Interactions:**

- Endogenous substances:

- The increase in free fatty acids and bilirubin (particularly in the newborn).

- Drug interactions:

- Competitive inhibition.
- Non-competitive inhibition.

B. Tissue diffusion of drugs

- Tissue diffusion corresponds to the distribution process (distribution) of a drug throughout the tissues and fluid compartments.
- Interacts with specific receptors, undergoes reactions of biotransformations and/or can be stored.
- State of equilibrium between the two free and bound tissue forms.

❖ Factors influencing tissue distribution :

***Plasma protein binding**

- Only the free fraction of a medicinal substance can diffuse towards the tissues.

Example: Salicylic acid, high albumin binding => Low tissue distribution.

***Physicochemical characteristics of the drug**

Only the fat-soluble and non-ionized fraction passes through the cell membrane of lipid-protein nature.

❖ Particular affinity of organs

For the same drug, the quantity fixed differs from one organ to another.

This can be explained by:

- A tropism towards the site of action.
- Metabolic and excretory activity.
- Chemical reactions between drugs and constituents of the body (tetracycline and bone).

❖ Organ irrigation and local blood flow

Tissues can be classified according to their vascularization:

- Richly vascularized tissues: heart, lungs, liver, kidneys, brain, endocrine glands.
- Moderately vascularized tissues: skin, muscles.
- Poorly vascularized tissues: marrow, adipose tissue.
- Very poorly vascularized tissues: bones, teeth, tendons, ligaments, cartilages, appendages.

The latter two represent a storage location with the possibility of reaching toxic concentrations in these tissues if the medicine is used long-term.

C. Storage of drugs in the organs

• Cellular reservoirs:

- Adipose tissue: Fat-soluble Md, exp; barbiturates. Tank enough stable due to its relatively low blood flow.
- **Bone tissue:** tetracycline adsorbs on the surface of the bone matrix.

Bone tissue can become a slow release reservoir of agent toxic: lead.

D-Redistribution phenomena

For certain fat-soluble drugs, distribution tissue can be so rapid and intense in certain organs at high blood flow, we witness a reversal of the concentration gradient with higher concentrations elevated in tissue than in plasma. This results in a redistribution of these drugs to the plasma.

Exp: thiopental will diffuse very quickly in the system central nervous system and induce rapid anesthesia but creating a concentration gradient such that this situation will quickly reverse and the thiopental will be eliminated from the brain.

II.1.C.Metabolism

Third stage of pharmacokinetics

- All enzymatic reactions undergone by PA also called Biotransformations.
- Transform the AP for the elimination phase.

Main organ concerned: the liver  Metabolites (inactive, active, toxic).

*Biotransformation refers to the various chemical **modifications** that undergo drugs in the body to give rise to one or more compounds, called **metabolites** which may be pharmacologically active, inactive or sometimes toxic.

Biotransformations are mainly carried out by **enzymatic reactions**.

Drug metabolism has two important consequences:

- The drug becomes more hydrophilic which accelerates its excretion through the kidneys.
- Activation of the original molecule (**pro-drug**).

A. Metabolism sites

The metabolism of drugs occurs mainly in the liver due to its rich vascularization and its richness in microsomal enzymes which play a primordial role in the biotransformation of drugs in the body. Other organs like the gastro tract intestinal, kidneys, lungs, skin, brain, placenta... can also intervene.

B. Importance of biotransformations in therapy

The biotransformations of drugs are important to consider and are sought during the study of a new drug because they determine:

⊗ **The route of administration:** proteases in digestive juice make administration impossible oral administration of many drugs with a peptide structure such as insulin.

⊗ **The dose and rate of administration:** a drug quickly transformed into inactive metabolites should be administered more frequently during the day. On the contrary, if inactivation is insufficient (elderly), the dosage must be reduced or the doses spaced out to avoid toxic risks by overdose.

* Allows you to avoid or benefit from interactions between administered medications simultaneously.

*Biotransformation reactions are divided into two types (Figure 6):

1-Phase I reaction / Functionalization

- **Oxidation:** are carried out at the microsome level using enzymes called cytochromes P450.

- **Reduction:** less frequent than oxidation, it also occurs at the microsome level thanks to enzymes called reductases.
- **Hydrolysis:** is carried out by enzymes called hydrolases located in the cytoplasm of cells.

*Drug metabolized by phase I reactions can give rise to active, inactive or toxic metabolites.

The oxidation reaction is the most common reaction. Other reactions are reduction and hydrolysis reactions. Microsomes are associated with oxidation reactions. Many enzymes involved in drug metabolism are located at the level of the smooth endoplasmic reticulum, a subcellular organelle which appears in the form of small vesicles in tissue homogenates. These vesicles called microsomes can be isolated by density gradient centrifugation.

Oxidation reactions at the microsome level involve the presence of NADP (in reduced form) (NADPH), oxygen and two key enzymes: (i) a flavoprotein, NADPHcytochrome P-450 reductase; and (ii) a cytochrome P-450 hemoprotein, which acts as an end-of-reaction oxidase. There are numerous subtypes (isoenzymes) of cytochrome P450 whose specificities differ depending on the substrate although cross-reactions are frequently observed (**Figure 4**).

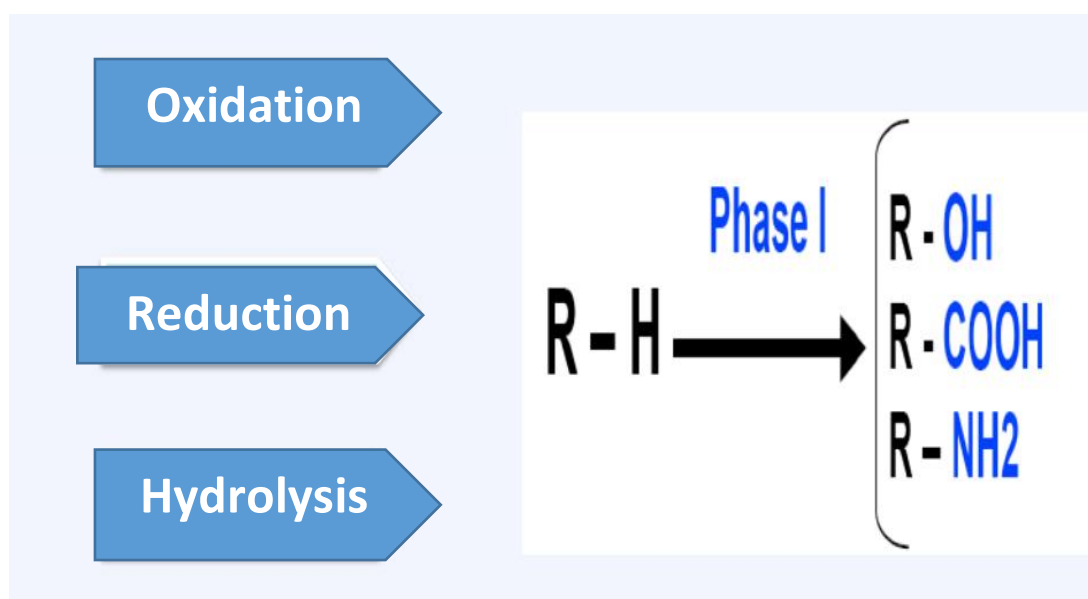


Figure.4. Phase I reaction / Functionalization [3].

2-Phase II reaction (Synthetic)

These reactions generally take place in the liver and involve the conjugation of the drug or its phase I metabolite to an endogenous substance. The conjugates thus formed almost always have lower activity and are polar molecules which are easily excreted by the kidney

The product formed called a conjugate is inactive and easily eliminated. The place of conjugation is essentially hepatic, these reactions are catalyzed by enzymes called transferases.

There are 6 types of conjugations: **glucuronide conjugation; sulfoconjugation; acetylation; methylation; conjugation to glutathione** and **conjugation to glycine** (it is an amino acid).

-Acetylation and methylation do not lead to polar compounds but serve to reduce or eliminate biological activity (**Figure 5**).

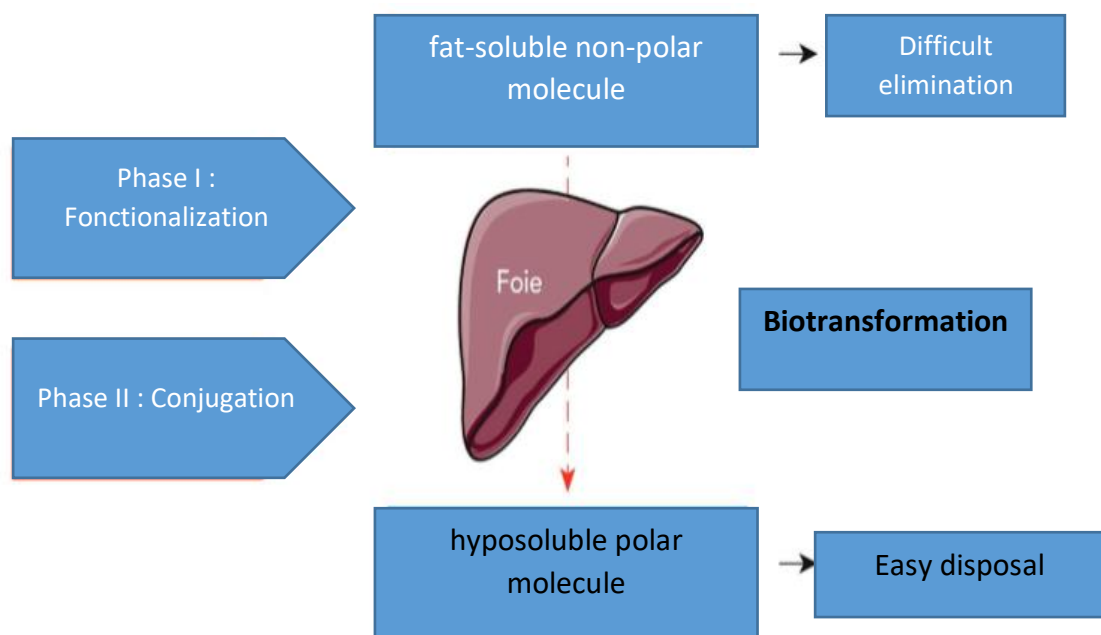


Figure.5. drug metabolism [4].

II.1.D. Elimination

Fourth step of pharmacokinetics

-Eliminate PA and its metabolites from the body.

*Bile duct.

*Pulmonary route.

*Renal pathway: functional unit: NEPHRON; elimination of drugs in urine.

➤ Disposal definitions

*Elimination constant: fraction of the quantity of the substance that is eliminated per unit of time.

*Half-life ($t_{1/2}$) [s]: time required to eliminate half of the substance.

*Total (or metabolic) clearance (Cl) [ml/min]: purified volume per minute.

A. Elimination assessment: The parameter that makes it possible to quantify the elimination process is: clearance.

A.1. Clearance concepts

Only the drug contained in the vascular compartment is purified when crossing an organ.

Plasma clearance is defined as “the volume of plasma completely cleared of the drug per unit of time. Clearance is measured in flow units: **L/h** or **ml/min**.”

We distinguish between organ clearance and total clearance.

A.2. Clearance of an organ

The clearance of an organ corresponds to the quantity of blood which passes through this organ and which will be completely free of the drug per unit of time. It is equal to the product of the blood flow (Q) in the organ by the extraction coefficient of the organ (E).

$$C = Q \cdot E$$

The extraction coefficient is calculated according to the following equation:

$$E = (C_a - C_v) / C_a$$

Where: C_a : concentration of the drug at the entrance to the organ.

C_v : concentration of the drug at the exit of the organ.

This coefficient allows drugs to be classified into three categories:

→ Medicines with a low extraction coefficient ($E \leq 0.3$).

→ Medicines with an average extraction coefficient ($0.3 < E < 0.7$).

→ Medicines with a high extraction coefficient ($E \geq 0.7$).

A.2. Total clearance

Total clearance (or body clearance or plasma clearance) is the result of all clearances that can be had in the body.

$$CL_{\text{total}} = CL_{\text{renal}} + CL_{\text{hepatic}} + CL_{\text{other}}$$

B. Hepatic elimination

At the hepatic level, two mechanisms contribute to the elimination of a drug: metabolism hepatic and biliary excretion. Hepatic clearance is therefore broken down into: hepatic clearance metabolism and bile clearance.

$$CL_{\text{hepatic}} = CL_{\text{metabolic}} + CL_{\text{biliary}}$$

B.1. Metabolic hepatic clearance

It depends on:

- The quantity of medication reaching the liver, which depends on blood flow sanguine.
- Binding to plasma proteins, since only the free fraction can be captured by the hepatocyte.
- Intrinsic clearance, i.e. the capacity of the liver to metabolize the drug, which depends of enzymatic activity.
- Hepatic extraction coefficient (E).

B.2. Bile clearance

✓ Characteristics of Bile Excretion

- ⊗ Biliary excretion mainly concerns large molecules (MW > 300) and metabolites conjugates.
- ⊗ It involves transporters at the level of biliary canicules.
- ⊗ The biliary elimination route is generally an accessory route. Certain medications however have a predominant biliary elimination (Ex: Erythromycin, Spiramycin, ampicillin, rifampin, etc.).
- ⊗ After excretion in the bile, the drug is found in the intestinal lumen: 2 possibilities: Fecal elimination or Reabsorption (enterohepatic cycle).

✓ **Enterohepatic cycle**

Process by which a drug passes through the liver where it is metabolized and then eliminated under conjugated form via the bile passes to the duodenum where it undergoes hydrolysis releasing thus the initial molecule which is then reabsorbed and joins the general circulation. This recycling leads to an increase in plasma concentrations.

C. Renal elimination

***Calculation of renal clearance:**

$$CL_{\text{renal}} = CL_{\text{filtration}} + CL_{\text{secretion}} + CL_{\text{reabsorption}}$$

It is possible to calculate an excretion ratio (Rex) which allows you to know if the PA is only filtered or if filtered, secreted (S) and reabsorbed (R).

$$\mathbf{Rex = CL_{\text{renal}} / CL_{\text{filtration}}}$$

Rex = 1 AP: only filtered and/or S=R.

Rex < 1 AP: filtered, secreted and reabsorbed with R>S.

Rex > 1 PA: filtered, secreted and reabsorbed with S>R.

D. Other routes of elimination

Other elimination routes are in the minority.

***Salivary elimination:** the elimination of certain medications can be done by salivary, which offers the possibility of a dosage.

E. Pulmonary elimination: it is important for volatile substances.

F. Factors of variation in the renal elimination of drugs: Certain pathophysiological or exogenous factors can modify the elimination of drugs.

➤ **Pathophysiological factors**

- **Renal insufficiency:** leads to a reduction in the elimination of drugs and promotes accumulation. The reduction in elimination is proportional to the degree of renal insufficiency, which can be measured by certain biological tests (creatininemia, creatinine clearance) dosage adjustment is necessary.

- **Heart failure:** leads to a reduction in renal blood flow.
- Any modification of protein binding of drugs, by increasing the free fraction, accelerates elimination.
- Age.
- **Exogenous factors:**
 - * **Change in urinary pH:** any change in urinary pH is likely to change passive tubular reabsorption, occurring on the non-ionized fraction of the drug:
 - The alkalization of urine reduces the reabsorption of weak acidic drugs.
 - Acidification of urine reduces the reabsorption of weak base medications.
 - * **Competition phenomena:** between drugs at the level of renal tubular secretion
Example: penicillin and probenecid.

II.2. Pharmacodynamics

Pharmacodynamic effect is a measurable and reproducible modification, functional or organic, caused by a drug in a biological system called an “effector” (**Figure 6**).

A drug causes one or more pharmacodynamic effects, for doses which may be different. A medicine has:

- **A main effect**, used therapeutically.
- **Side effects**, which may be useful or indifferent or annoying or harmful. The same pharmacodynamic effect can be caused by several drugs; all of these drugs constitute a pharmacological family (A pharmacological family is made up of all of the drugs having a common pharmacodynamic effect).

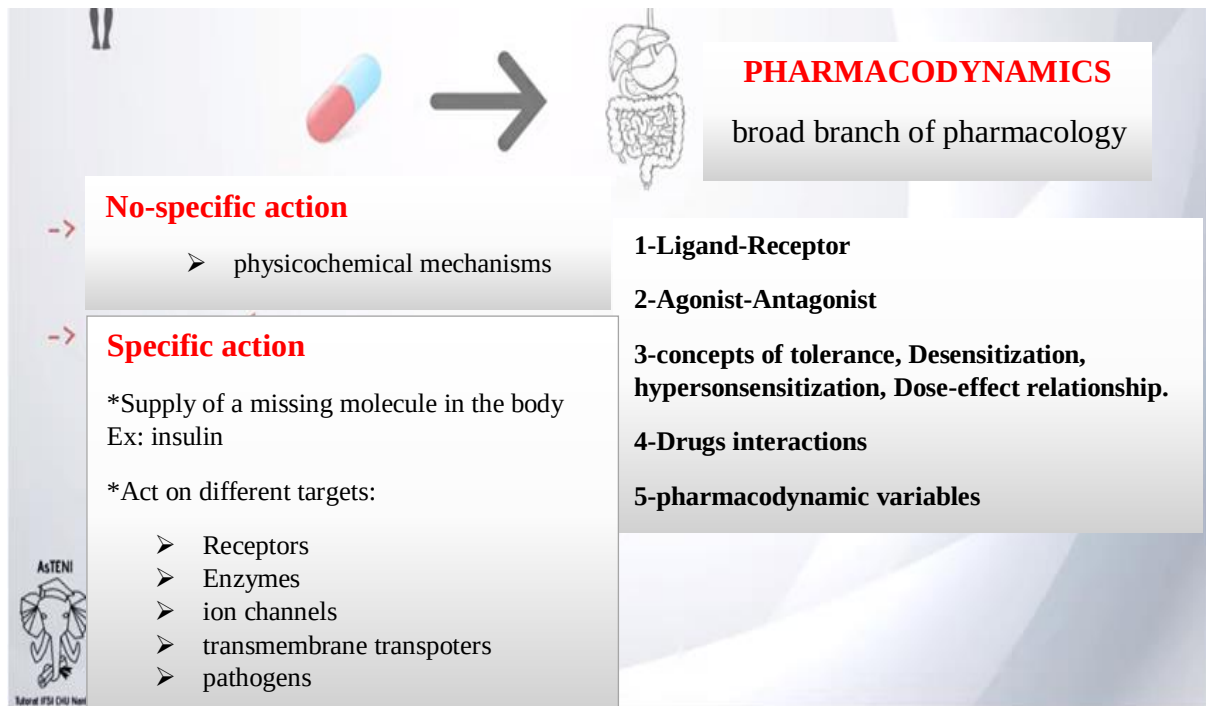


Figure.7.Pharmacodynamics, the action of the drug in the body [5].

II.2.1. LIGAND-RECEPTORS

-Organism —→ Number of receptors.

*Located in various locations.

*Different types.

*Allows multiple actions.

Receptors= Target of drugs

-Receptors:

-Part of the cell.

-Receives extra-cellular signals.

Different natures: Hormones, Neurotransmitters and drugs (**Figure 7**).

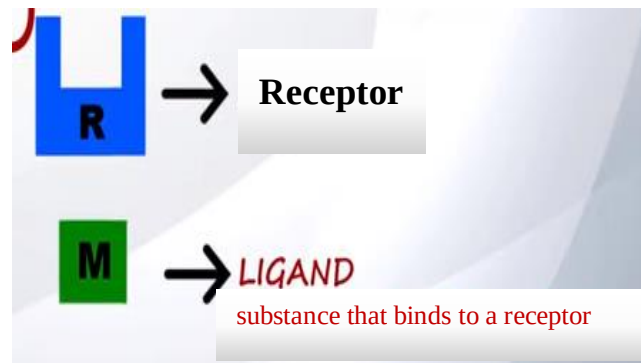


Figure.7. Ligand-Receptor [5].

II.2.2. Agonist-Antagonist

Linked to the concept of **ligand(s)-receptors**

***AGONIST:** Effect of the exogenous agonist ligand (active principle) = biological effect of the endogenous ligand (example: hormone).

***Antagonist:** inactivates or blocks the receptors (prevents the agonist ligand from attaching to the receptors example: the antidote for Morphine is NALOXONE, in other words it is its antagonist).

II.2.3. Tolerance, Desensitization, Hypersensitization and dose-effect relationship

Tolerance: desensitization of receptors.

Desensitization: Reduction in the number of receptors.

Hypersensitization: increase in the number of receptors.

Dose-effect: increase in pharmacological effects proportional to the dose administered.

Allows you to predict 2 types of relationships:

*Dosage/therapeutic effects.

*Dosage/adverse effects.

II.2.4. Drugs interactions

- Multiple medications administered at the **same time** to the **same patient** → Risk of modification: therapeutic effect and toxic effect.

II.2.4.a. Synergistic interactions: Addition of the pharmacological effect can be **PARTIAL** or **TOTAL POTENTIALIZATION**.

* **Addition** ++++ of therapeutic effects.

II.2.4.b. Interaction by antagonism

*Therapeutic effect of drug A deduced by those of drug B: linked to the AGONIST-ANTAGONIST relationship can be PARTIAL or TOTAL (=Pure antagonist) (**Figure 8**).

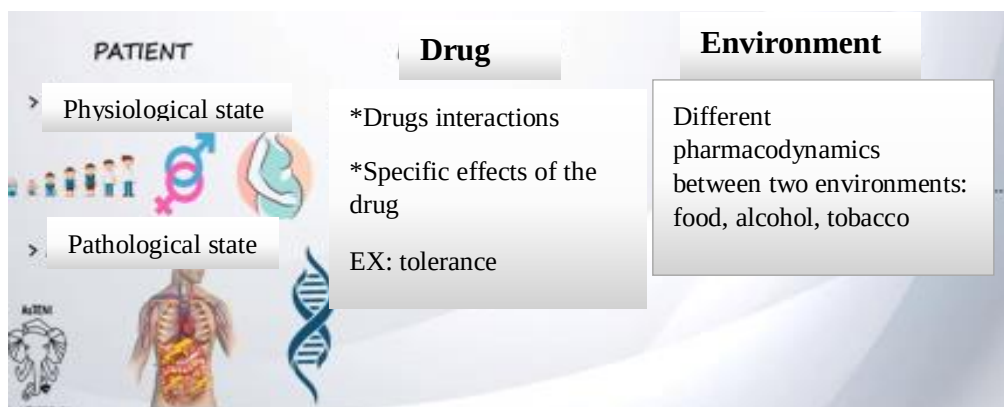


Figure.8. Pharmacodynamic variables [5].

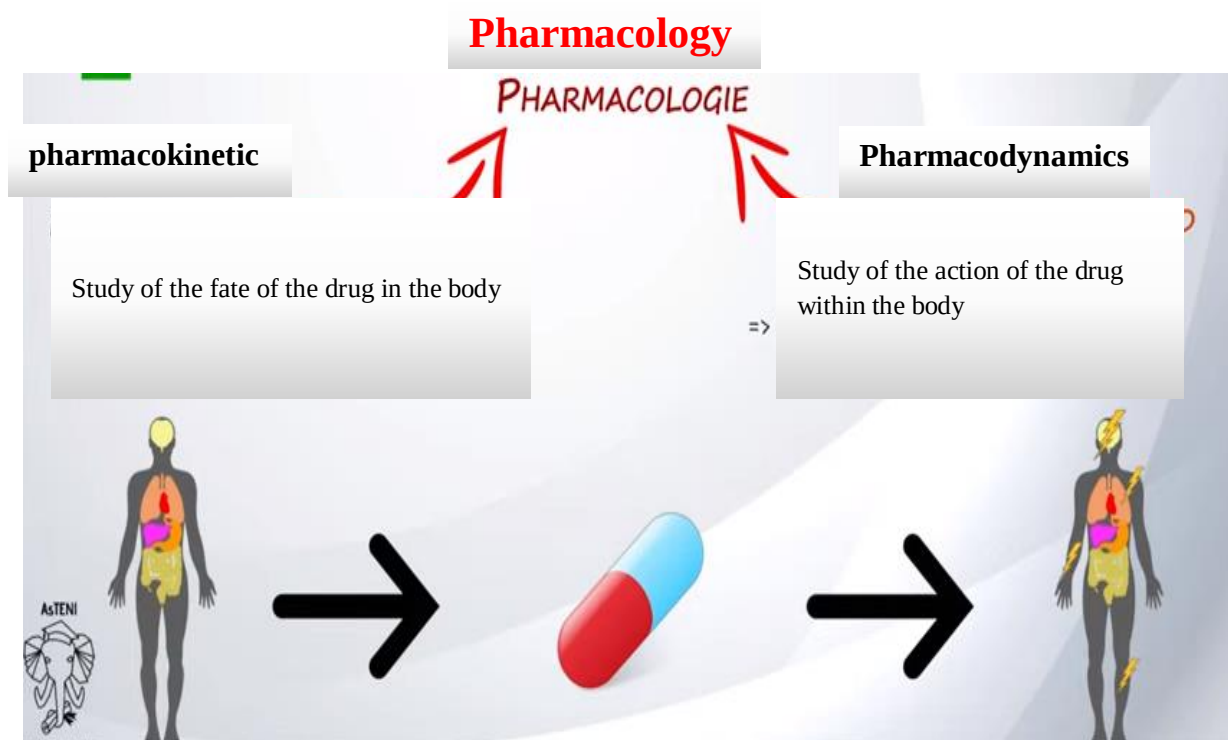
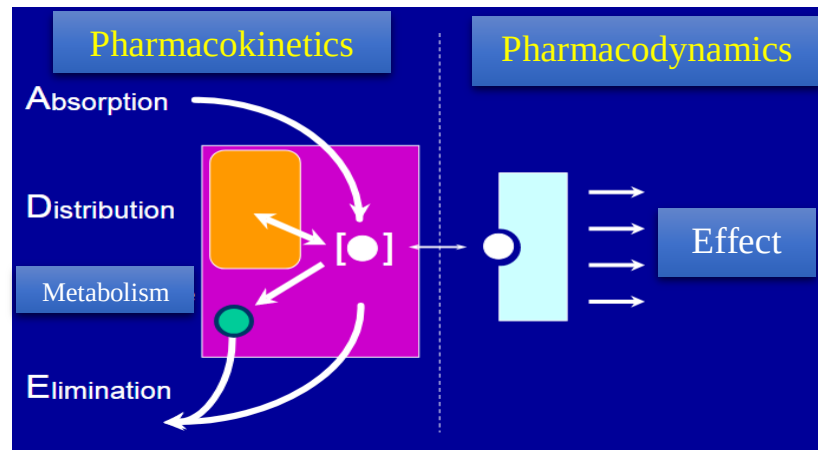


Figure.9. Pharmacokinetics and pharmacodynamics [5].

Pharmacokinetics/ Pharmacodynamics



9

Figure.10.The relationship [5].

II.3. Pharmacovigilance

It is the study of methods for detecting and preventing adverse effects

- ☐ Adverse reaction: a harmful and unwanted reaction occurring at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or modification of physiological function, or resulting from misuse of the drug or product.
- ☐ Serious adverse reaction: an adverse reaction that is lethal, or likely to be life-threatening, or results in disability or incapacity, or causes or prolongs hospitalization.

Exercises

Exercise I

After intravenous injection of a dose of 50 mg/kg of a drug to a patient, the following plasma concentrations were measured (in mg.L^{-1}) as a function of time (in hours): Time 0: 3.45 Time 1 hour: 2.55 Time 2 hours: 1.65 Time 4 hours: 0.75 Time 8 hours: 0.15

Question 1: Draw the concentration curve as a function of time.

Question 2: Give the plasma concentrations for Times 3 and 6 hours.

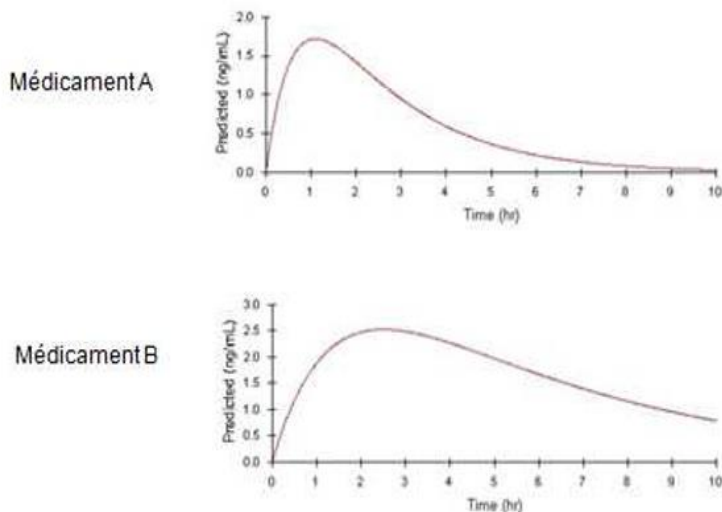
Question 3: Calculate the distribution volume. **Question No. 4:** Describe the elimination half-life.

Exercise II

Orally, two drugs (10ng A) and (15ng B) were administered to a patient (50KG), according to the concentration versus time curves of the drugs (A) and (B).

Question 1: Compare the pharmacokinetic profile of the two drugs.

Question 2: Calculate the half-life and volume of distribution of each drug.



Exercise III

25 mg of a drug is administered to a 50 kg patient, i.e. 0.5 mg/kg (or 500 $\mu\text{g/kg}$) and its volume of distribution is measured at 40 l/kg and the following plasma concentrations were measured (in $\mu\text{g.L}^{-1}$) as a function of time (in hours):

Time 1 hour: 8.55 Time 2 hours: 4.65 Time 4 hours: 1.75 Time 8 hours: 0.15.

Question 1: Calculate the C_0 and Half-life.

Answers

Solution I

Concentrations ($\text{mg}\cdot\text{L}^{-1}$) on the ordinate and time in hours on the abscissa On the plot of the area under the curve (ASC or AUC)

C at time 3h: 1mg/l

C at time 6h: 0.25mg/l

VD: $\text{dose}/C_0 = 50/3.14 = 14.5 \text{ l/kg}$

$T_{1/2} = 1.8\text{h}$ Corresponding to half of the plasma concentration eliminated on the plot of the area under the curve (AUC or AUC): $3.45/2 = 1.72\text{mg/l}$

Solution II

Profile Comparison

T max: faster for A than B (1 hour versus 2.5 hours)

C max: higher for B than A (2.5 ng/ml versus 1.7 ng/ml)

Medicine A: $\text{VD} = \text{dose}/C_0 = (10/50)/0.25 = 0.8\text{ml/K}$ $T_{1/2} = 3\text{h}$ corresponding to $1.7/2 = 0.85\text{ng/ml}$ Bioavailability 1.7 corresponding to 17% of the concentration external and at 1 hour

Drug B: $\text{VD} = \text{dose}/C_0 = (15/50)/0.25 = 1.25\text{ml/K}$ $T_{1/2} = 8\text{h}$ corresponding to $2.5/2 = 1.25\text{ng/ml}$ Bioavailability 2.5 corresponding to 16.7% of external concentration and at 2.5 hours

Solution III

C_0 : Dose divided by volume of distribution $500/40 = 12.5\mu\text{g/l}$

$T_{1/2} = 1.5\text{h}$ Corresponding to half of the plasma concentration eliminated on the plot of the area under the curve (AUC or AUC): $12.5/2 = 6.25\mu\text{g/l}$

Chapter III: Toxicology

III.1. General concepts in toxicology

➤ Toxicology

Toxicology has long been recognized as the science of poisons. She studies the harmful effects of toxic products on living organisms, such as their properties and mode of action. It draws on a multitude of scientific knowledge and is interested in several sectors of human activity, notably agriculture, food, the pharmaceutical industry, the cosmetics industry and the environment.

Science that studies:

*Poisons, toxic, pollutants.

*Their origins.

* Their detections and dosages.

*Means of treatment and prevention against these molecules.

➤ Toxicity

Character of chemical substances which, upon contact with or after penetration of the body, have the property of causing dysfunction at the molecular, cellular or organic level.

➤ Toxic or poison

A poison, or toxic product, is a substance capable of disrupting the normal functioning of a living organism. It can be naturally present in the environment (e.g.: dust, pollen, asbestos) or be mainly produced by human activities (e.g.: welding fumes, crystalline silica dust emitted following blast cleaning). abrasive, etc.). The toxic product can be chemical (e.g.: acetone) or biological (e.g.: mold, aflatoxins, viruses). Toxic products, including chemicals, are an integral part of our lives. Scientific and technological development is accompanied by the marketing and increased use of these products, the diversity and quantity of which are only increasing, as is the number of people exposed to them. They are found in the air we breathe, in our food, our medicines, our cosmetics, etc. We are frequently exposed to it in our leisure time and in our workplace

➤ Xenobiotic

Substance foreign to living matter: it is an exogenous substance.

➤ **Origin**

- * Household products.
- * Gas polluting the air.
- * Waste polluting drinking water.
- * Toxic plants: plants, mushrooms.
- * Medicines.
- * Food.
- * Hygiene products.

The important thing is the dose: “All things are poison, and nothing is without poison; only the dose makes something not a poison. » Paracelsus 1533.

III.2. Classification of toxicants

Among the numerous classifications proposed, the most important are those based on: the chemical nature of the compound, the mechanism of toxic action, the use or finally the nature of the danger

III.2.1. Depending on the chemical nature we distinguish:

- Gaseous toxicants: Carbon monoxide, ammonia, sulfur dioxide.
- Toxic minerals: Metalloids (arsenic, phosphorus), metals (mercury, lead, cadmium).
- Organic toxicants: Alcohols, phenols, heterocyclic compounds, alkaloids, glycosides

III.2.2. According to the mechanism of toxic action

The mechanism of action of all toxicants is unfortunately not known. The following mechanisms of action are interesting to consider

➤ **Caustic toxicants**

Concentrated acids and bases, phenols, halogens, some heavy metal salts denature proteins and cause irreversible damage to all cells with which they come into contact.

They cause chemical burns, very similar to thermal burns. The skin and mucous membranes are the most exposed tissues.

Mineral derivatives of arsenic, especially trivalent derivatives (arsenites) exert a caustic-necrotic action on the digestive mucous membranes, causing ulceration and necrosis in the stomach and intestine.

Lead, after single ingestion of high quantities, causes a caustic action on the digestive tract. At lower and repeated doses, it causes damage to the renal proximal tubes.

Paraquat (herbicide) is extremely irritating to the oral, pharyngeal and digestive mucous membranes.

➤ **Thioloprivate toxicants**

These toxic substances (As, Pb, Hg) attach to the thiol - SH groups of sulfur-containing amino acids or enzymes, thus inhibiting their activities. This enzymatic inhibition can be lifted by administration of compounds rich in groups - SH (dimercaprol, D penicillamine) for which these metals have a greater affinity (chelators). The complex thus formed is water-soluble and therefore easily eliminated by the kidney.

➤ **Methemoglobinizing toxicants**

Nitrates and nitrites, chlorates, paracetamol in cats. They oxidize ferrous iron (Fe^{++}) in hemoglobin into ferric iron (Fe^{+++}), which is unsuitable for oxygen transport, causing death through cellular anoxia.

➤ **Convulsant toxicants**

This is the case for strychnine, metaldehyde and crimidine.

➤ **Anti-cholinesterase toxicants**

Organophosphate insecticides and carbamates have a high affinity for cholinesterases and compete with acetylcholine which is their natural substrate. The organophosphates are hydrolyzed: but part of their molecule remains attached to the cholinesterases which are thus gradually inhibited. Acetylcholine is no longer destroyed immediately after release into the nervous system and accumulates in the body causing toxic manifestations.

➤ **Toxicants causing abnormal biosyntheses**

Lead acts on the biosynthesis of heme, from succinyl coenzyme A. Lead disrupts the biosynthesis of porphyrins by opposing the condensation of two molecules of delta amino-levulinic acid to form porphobilinogen, then slowing it down. the transformation of coproporphyrins into protoporphyrins and of protoporphyrins into heme.

➤ Other toxic manifestations

Other manifestations of toxicity revealed by experimental studies (irritant power, allergenic action, hepatic, renal, blood damage, etc.) must also be taken into consideration for the assessment of the toxic risk.

III.3.Dose-response relationship

Researching the dose-response relationship of a molecule is essential to obtain quantitative information on the importance of the pharmacological effect and to compare different molecules with each other.

The dose-response curve forms an asymptotic curve that can be transformed into a sigmoid using semi-logarithmic coordinates. The measured effect can be expressed as an absolute value or as a percentage of the maximum effect (**Figure 11**)

In clinical pharmacology, it can also be used to establish the relationship between dosage and therapeutic effect or between dosage and adverse effects.

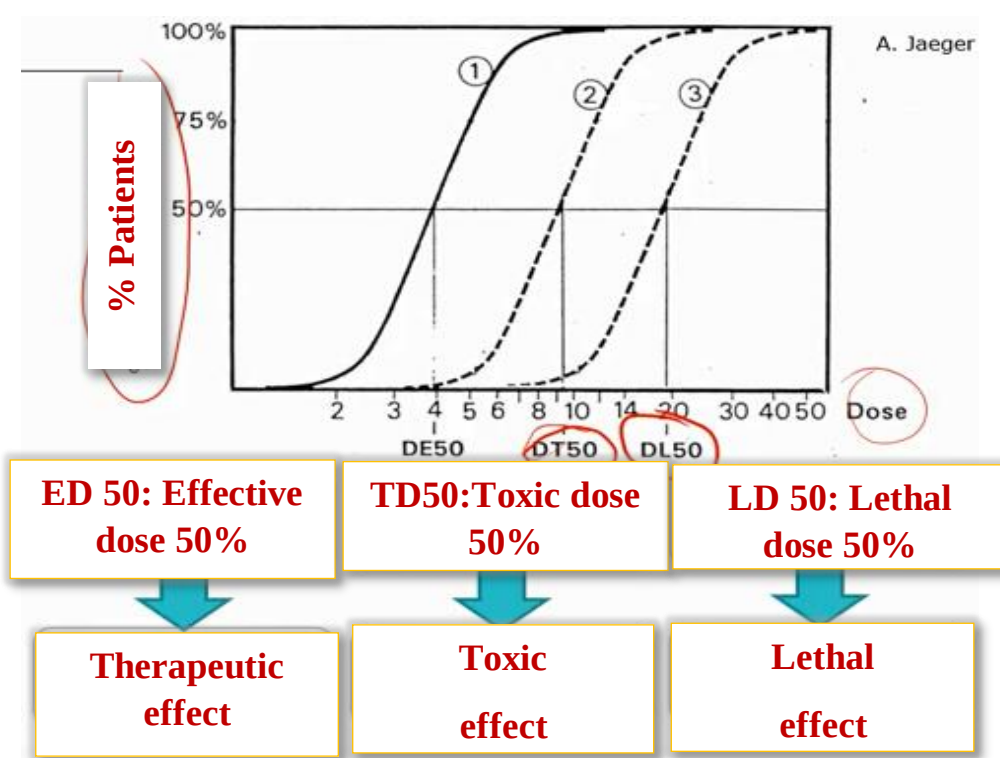


Figure.11. Dose-response relationship [6].

The **ED50** (effective dose 50): dose of agonist which allows 50% of its maximum effect to be obtained.

The **LD 50**: This is the minimum dose of substance capable of killing an animal by slow intravenous administration; death is assessed by cardiac arrest. This dose allows the experimenter to choose the doses to use for the LD50.

III.4. Different types of toxicity

Any substance is toxic. This toxicity varies depending on the quantity, exposure time and the physiological state of the patient. Let's see the different factors linked to these toxic effects as well as the different toxicities observed. (**Figure 12**)

Toxicokinetics: descriptive and quantitative study of the fate of toxic substances in the body, equivalent to pharmacokinetics in the case of medicinal substances.

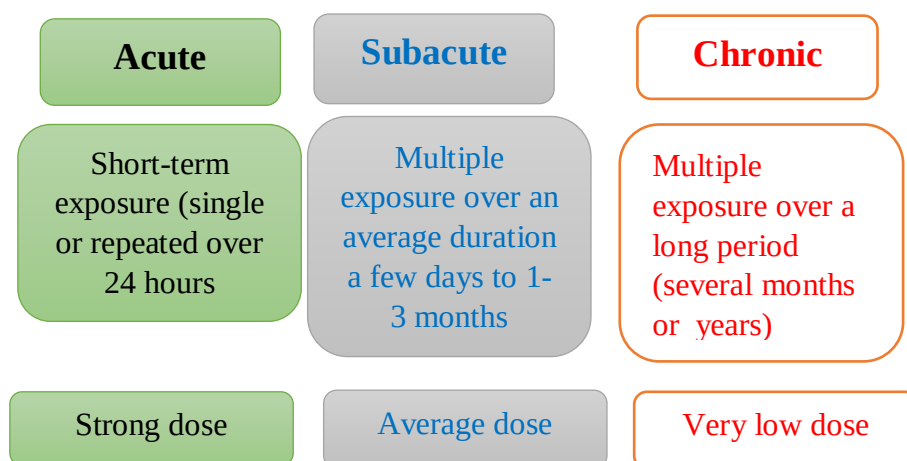


Figure.12. Types of toxicity [7]

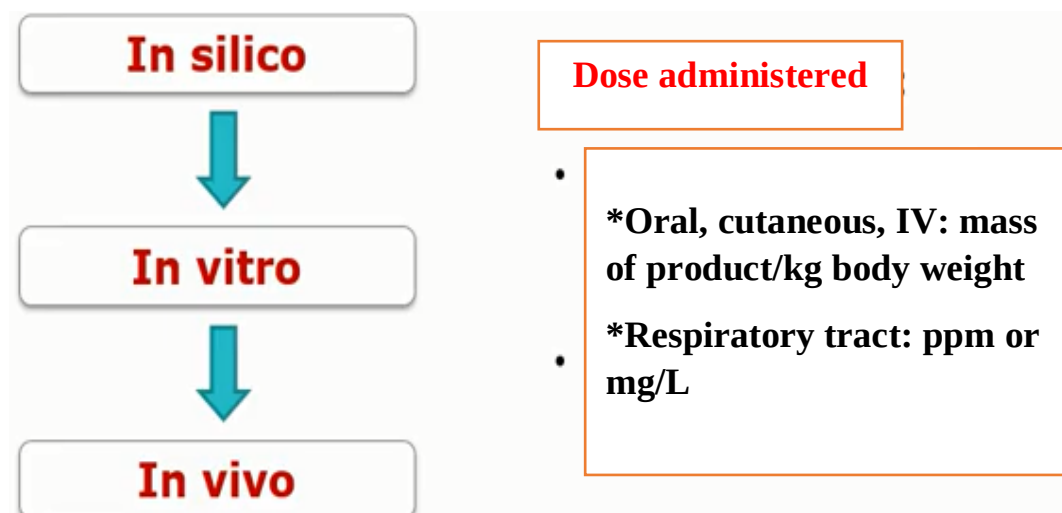
III.5. Difference between exposure and effect

Acute poisoning is a harmful effect that appears quickly following a single or short-term exposure (minutes, hours). This is, for example, a skin burn following contact with an acid. If, on the contrary, the harmful effect is the consequence of long exposure (several days to several years) or repeated exposure, it is said to be chronic, as in the case of cancer. Indeed, toxicity then results from the gradual accumulation of the toxic product, its metabolisms or the damage caused by them in the body. The distinction between acute exposure and acute effect as well as between chronic exposure and chronic effect is often difficult to establish. Acute exposure may cause a chronic effect. Conversely, repeated exposure over years can cause short-term effects, such as respiratory or skin sensitization. Thus, the links between exposure and effect are not necessarily predictable. (**Table 3**)

		Effect	
Exposition		Acute	Chronic
	Acute	Short-term effect following short-term exposure Ex: skin irritation following contact with acid.	Long-term effect following short-term exposure Ex: persistent respiratory disorder following inhalation of a high concentration of chlorine.
	Chronic	Short-term effect following long-term exposure Ex: skin sensitization to ethylene diamine following repeated contact over several years.	Long-term effect following long-term exposure : liver cancer caused by oral exposure to ethanol over several years.

Table.3. Difference between exposure and effect [7].

III.6.Toxicity study method



III.7. Areas of study of toxicology

III.7.A. Forensic toxicology

This is the first area to differentiate poisonings: criminals Intentional or accidental.

III.7.B. Industrial toxicology

It is linked to occupational medicine.

***Asbestos:** occupational disease called **asbestosis** (employees in building construction, shipbuilding sites, etc.).

***Lead:** Lead poisoning and the disease corresponding to lead poisoning. There are multiple sources of lead contamination: **exhaust gases** from **vehicles** with leaded gasoline engines, lead residues from **industrial production** passing through water, air and soil. They mainly expose workers in heavy industry, construction and **automobiles**.

III.7.C. Drug toxicology

The toxicity of the active ingredient is studied during its design and is part of the Marketing Authorization file. During manufacturing, industrial toxicology is monitored. After Marketing Authorization, pharmacovigilance lists the problems caused by medical prescriptions.

III.7.D. Food toxicology

She studies :

a-Foods that are toxic by nature: Mushrooms, plants, etc.

b-Somes foods that become toxic due to their normal production conditions: canned tuna.

c- Foods becoming toxic due to poor storage conditions: Acid+metal from cans.

-Foods additives included on a positive list defined by the health authorities: Flavor improvers: sodium glutamate in Chinese cuisine for example.

III.7.E. Agricultural toxicology

Pesticides and fertilizers present a risk for the agriculture that applies them but also for the consumer through the persistence of the products in food.

Example: organochlorines and organophosphates.

III.7.F. Ecotoxicology

It is the study of the toxic effects of chemical or **physical** agents on organisms and communities, and of the transfer pathways of these agents, as well as their interactions with the environment.

It is therefore the study of the ecological consequences of **environmental pollution** by toxic substances.

III.7.G.Regulatory toxicology

Regulatory toxicology is that practiced to obtain marketing authorizations (AMM) for different products that may prove toxic, such as pesticides, GMOs, or other food additives...it is applied, finalized research. The practices of such toxicology “were initially forged in relatively small circles of pharmacologists and industrial hygiene specialists who worked closely with users of their evaluations: industrial associations (to establish working conditions with safe exposures to chemical substances).

Note:

A medicine meets the definition of a xenobiotic because it is neither an endogenous substance nor a food intended to ensure growth or energy expenditure for the body. It is indeed a substance foreign to life.

III.8.Dose and modulation of toxic effects

a) The maximum dose

During the tests the maximum dose is determined. Beyond this dosage, side effects appear and threaten the health of the sick person or not.

b) The notion of therapeutic margin

This therapeutic margin is defined by the difference between the maximum dose producing a therapeutic effect and the dose at which side effects appear within the treated population.

III.9. The fight against intoxication

III.9.1.Treatment with the antidote

Any substance or technique that counteracts the onset or reduces the duration or intensity of toxic effects is an antidote.

Example

Morphine: **Naloxone**

Benzodiazepine: **Anexate.**

Chapter IV: Drug poisonings

IV.1.Introduction

***Represents between 20% to 60% of admissions to emergency departments.**

***Mortality is low: 0.5 to 1% (resuscitation for the most serious).**

***Require immediate treatment and urgent measures to be taken.**

Most often, poisonings are due to taking (in descending order): benzodiazepines, analgesics, antidepressants, neuroleptics, carbamates, barbiturates and psychotropic drugs.

Drug poisonings can cause any type of symptom depending on the drug involved.

IV.2. Circumstance of occurrence

- **Voluntary** with suicidal intent, even drug addiction: very common 80%.

-**Accidental:**

*Children under 6 years old (domestic accident).

*Therapeutic error: dose/Kg problem for the child.

*self-medication in adults and errors in the elderly (vision, Alzheimer's, etc.).

*Renal (or even hepatic) insufficiency = accumulation by non-elimination.

-**Criminals:** but rare.

Risk :

-Immediate: cardio-respiratory arrest, respiratory distress, etc.

IV.3.Symptomatic treatment

-Life-saving measure: treat cardio-respiratory or neurological distress.

-oxygen if breathing problems.

-warming or fight against hypothermia....ect

IV.4.Toxicological treatment

GOALS:

1. Prevent further intoxication.
2. Fight against the action of the toxic agent.
3. Increase the elimination of the toxicant.

IV.4.1. Prevent further poisoning:

The toxicant must be eliminated from its point of entry:

*Intravenous or Tissue Route: there is not much we can do

*Eyes: prolonged eye washing with physiological serum or water.

*Skin: undress the patient, wash with water.

*respiratory: evacuate to the open air; ventilate if necessary.

*Digestive tract: absorption depends on time, quantity, toxicant.

a-Provoked vomiting: only in conscious patients

b-Gastric lavage: very common, in cases of massive poisoning; even late

*gastric tube, in sitting position if conscious.

*in lateral position if consciousness is disturbed.

*volume of 10l of lukewarm water + 4g NaCl/l in adults.

*within 6 hours after ingestion and even later.

Contraindicated if caustic, hydrocarbons, foaming products

Never give milk in poisonings

Milk is fat suspended in water. Toxic substances circulate in the blood even better when there is fat in the stomach and are fixed even better where the fat is. Particularly in the brain.

c-Prevent the absorption of toxic substances: use of activated charcoal (carbomix*)

*adsorbs water and fat-soluble bodies on its surface.

*reduces the quantity of free toxic matter in the intestine and avoids the enterohepatic cycle.

*by gastric or oral tube: 50 to 100g in adults; 1g/Kg child

* risk of severe pneumonia if inhaled.

IV.3.2. Fight against the action of toxic

We will neutralize the toxicant or fight against its actions: **Antidote** (neutralize the product) or **antagonist** (against its effects).

Example: anaxate: perfect benzodiazepine antagonist.

IV.3.3. Increase the elimination of the toxic

-Fecal elimination: intestinal washing/laxatives (Mg salts).

-Urinary elimination: osmotic diuresis; if the toxicant is **renally eliminated**

A. Poisoning by Benzodiazepines

Definition : Benzodiazepines are molecules that act on the central nervous system, are a class of organic compounds formed from a **benzene** ring fused to a **diazepine** ring. And which have **5 fundamental properties** but at different levels depending on their chemical structure (**Figure 13**):

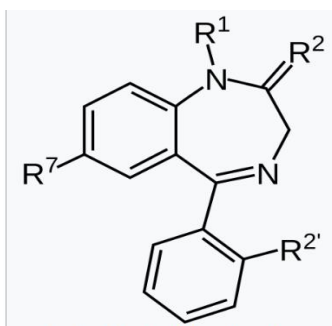


Figure.13. Structural formula of benzodiazepines [11].

1-Amnesiacs: which promote memory loss.

2-Anxiolytics: which act against anxiety.

3-Sedatives and hypnotics: which induce sleep.

4-Myorelaxants: which relax the muscles.

5-Anticonvulsants: which treat or prevent convulsions; which treat or prevent seizures.

Example: Diazepam, Clonazepam, Clobazam.

Induce strong drug dependence.

***Toxicokinetics**

-Rapid digestive absorption; plasma peak reached in 0.5 to 3 hours at therapeutic dose, delayed after ingestion of a massive dose.

-High liposolubility, hence wide diffusion.

-Cannot be eliminated in the native state by the kidney fat-soluble agents (therefore all undergo hepatic biotransformation).

-**Hepatic metabolism** with, for certain molecules, formation of active metabolites, hence the prolonged action.

-Elimination half-life varies greatly depending on the molecule (3 to 70 hours).

-Very slow elimination in elderly patients.

*** Toxic doses**

Adult : 0.1 à 0.5 g.

Child : 0.001 à 0.005 g/Kg.

*** Treatment**

- **Symptomatic treatment**

-No systematic gastric lavage.

-No benefit from renal or extrarenal purification.

-Oral charcoal 40 to 50 g

- **Specific treatment**

Antidote: Flumazenil; Anexate

- Injectable: 5ml/0.5mg

- (Maximum total dose = 2 mg)

- Adverse effect: convulsion, digestive signs, tremors, etc.

B. Poisoning by medicinal carbamates

✓ **pharmacological action**

Medicinal carbamates have sedative, anxiolytic and muscle relaxant effects; they are a family of organic compounds carrying an $R\text{-HN}(\text{C}=\text{O})\text{O-R}'$ function. These are in fact substituted esters of carbamic acid or a substituted amide (**Figure 14**).

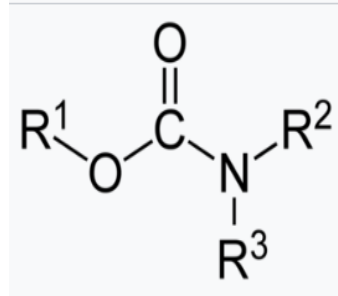


Figure.14. Chemical structure of carbamates [12].

✓ **Toxicokinetics**

- Variable and irregular digestive absorption.
- Half-life extended from 6 to 16 hours in case of massive ingestions.
- Hepatic metabolism with formation of inactive metabolites.
- Renal elimination.
- Total elimination in 48 to 72 hours.

Toxic dose: in adults: 4g.

✓ **Treatment**

1) Pre-hospital phase

-Symptomatic treatment: O_2

In the absence of beneficial effects catecholamines (adrenaline).

-No antidote.

2) Hospital phase

-Qualitative and quantitative blood dosage of carbamates.

-Activated charcoal within one hour of ingestion in the absence of contraindication.

C. Poisoning by tricyclic antidepressants

❖ **Toxicokinetics**

-Rapid gastrointestinal absorption but can be considerably slowed down due to **anticholinergic** effect.

-Very variable half-life: between 10 and 80 hours.

-Hepatic metabolism

-Enterohepatic cycle

-Elimination is urinary in unchanged form or metabolites.

❖ **Toxic dose**

Adulte : 500 mg Kg

Child : 5 à 10 mg/Kg

-Severe risk from 1g.

❖ **Treatment**

1) Pre-hospital phase

- Symptomatic treatment.

-Intubation and ventilation.

-Medical transport and hospitalization.

2) Hospital phase

-Hospitalization with symptomatic treatment: **oxygenation**

-Hemodynamic and cardiac monitoring.

-Gastric lavage in the first hour after ingestion.

D. Paracetamol poisoning

It is the most commonly used medication for pain and fever in the world (**Figure 15**).

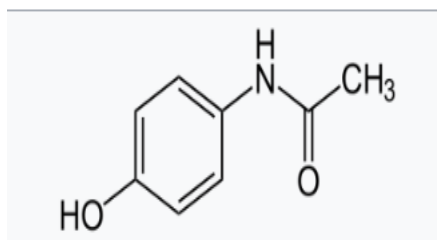


Figure.15. Chemical structure of paracetamol [13].

Properties

Analgesic and antipyretic.

Massive use: deadly

Antidote: N-acetyl-cysteine FLUIMICIL*

Toxic dose

Toxic dose for a 10 g intake in adults.

Pharmacokinetics and toxicokinetics

Quickly absorbed (digestive absorption: < 2 h, small intestine), metabolized by the liver in the form of derivatives which can be toxic to the liver itself and the kidneys in the event of an overdose. Peak plasma: 15 min to 2 hours, delayed in case of toxic intake.

Half-life: 1h_{1/2} to 3 hours.

E. Acute Ethyl Poisoning

➤ **Pharmacological properties**

The main **psychoactive** substance consumed in Western countries is “binge drinking” among young people: massive and rapid intake of the product with serious somatic consequences.

Rare accidental poisoning in adults.

➤ **Toxicokinetics**

-Rapid digestive absorption; plasma peak reached in 30 min

-Speed of absorption favored by gastric vacuity and gaseous nature of the drink.

-Hepatic metabolism (90%); there is gastric and intestinal metabolic activity.

➤ Treatment

1) Pre-hospital phase

-Sufficient symptomatic treatment most of the time, up to intubation – mechanical ventilation with O₂.

2) Hospital phase

-Routine blood testing

-Decrease in blood alcohol content: 0.15 to 0.45 g/1h

*If hypoglycemia: glucose solution

*If chronic alcoholism: vitamin therapy vit B1 (thiamine) 300 to 500 mg/j.

F. Barbiturate poisoning

Barbiturates are a class of depressant drugs that are chemically derived from barbituric acid (Figure 16)

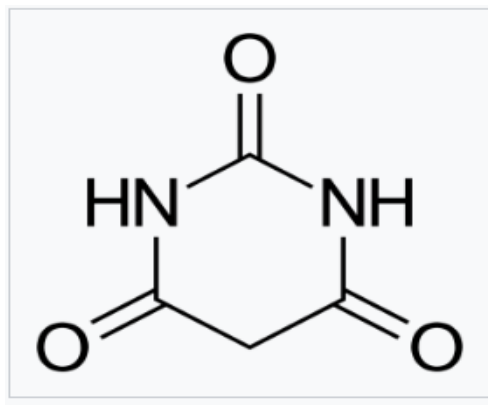


Figure.16. Barbituric acid, the parent structure of all barbiturates [14].

✓ Main risks

-Coma

-Respiratory depression.

✓ Pharmacokinetics

In pharmacology, there are two groups of barbiturates: long-acting phenobarbital on the one hand, and intermediate and rapid-acting hypnotic barbiturates on the other.

Peak plasma: adult 8h.

Half-life: adult: 84-160 hours.

Toxic dose: adult: 500mg/child: 20mg/Kg.

✓ **Treatment**

1. Oxygenation
2. Gastric lavage if seen within the hour and activated charcoal.
3. Simple reheating

G. Opiate poisoning (Morphine, heroin, codeine)

- **Clinical**

- Consciousness disorder.
- Respiratory failure.
- Bronchopulmonary infection
- Coma, convulsion.
- Hypothermia.

- **Treatment**

This is a life-threatening emergency. The essential objective is the correction of acute respiratory failure.

- **Specific antidote:** naloxone (Narcan) (pure and specific antagonist of opioid derivatives) 0.2 mg.

H. Cocaine poisoning

Can be administered in several forms

-Coca leaf, chewed; coca paste, smoke, pure Cocaine; the Hydrochloride form “snorted” or dissolved in water and injected intravenously, the free base form (“crack” or “free base”: smoke (**Figure 17**)).

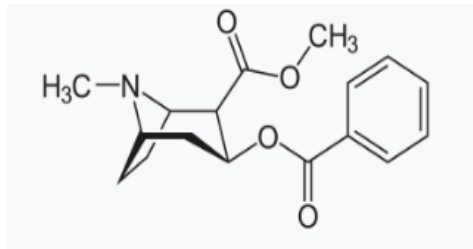


Figure.17. Chemical structure of Cocaine [15].

❖ Pharmacokinetics

- Action mechanism
- Blocking dopamine reuptake.
- Blocking of norepinephrine reuptake and increase in its synthesis.
- Inhibition of serotonin reuptake.

❖ Toxicokinetics

- The speed of absorption depends on the route of administration: instantaneous for the intravenous route, 10-15 seconds for the pulmonary route (crack), 30 to 60 min for the oral routes (coca paste) and nasal (hydrochloride).

-Oral route

- Resorption by the oral and gastrointestinal mucosa.
- Appears in the blood 30 to 60 minutes after taking.

-Nasal route

Hydrochloride form, very rapid resorption by the nasal mucosa, plasma peak in 30 to 60 minutes.

Chapter V : non-drug poisonings

V.1. Carbon monoxide

Carbon monoxide (CO) is a **colorless, odorless, highly diffusible gas**, with a density close to that of air and very toxic. It is produced during the incomplete combustion of any substance containing carbon atoms (fire of carbonaceous materials, large volcanic eruptions, industrial, urban, tobacco and domestic pollution).

V.1.2. The mechanism of CO poisoning

CO binds 85% to hemoglobin in the blood, for which it has an affinity more than 200 times greater than that of oxygen in humans. It forms a reversible combination with hemoglobin: carboxyhemoglobin (HbCO). A certain proportion of the hemoglobin in the blood is thus rendered incapable of playing its role as an oxygen vector in the body. CO can also combine with other hemoproteins such as muscle myoglobin (estimated at approximately 20% of absorbed CO).

V.1.3. CO poisoning and elimination

Anemic subjects, those with respiratory and coronary insufficiency are particularly sensitive to the effects of CO. The effects of CO on the human body essentially depend on the duration of exposure and the CO levels breathed.

Poisoning can be acute and accidental or subacute and chronic if the cause of the intoxication is not identified. Death generally occurs when the percentage of HbCO in the blood exceeds 60% of the hemoglobin originally present.

The elimination of CO occurs in unchanged form in exhaled air. Spontaneously, the half-life of CO in ambient air is around 4 hours.

V.2. Hydrocarbons

Hydrocarbons represent the vast majority of organic solvents.

An organic solvent (SO) is a liquid which has the property of dissolving, suspending or extracting other substances without causing chemical modification of these substances and without modifying itself. SO make it possible to apply, clean or separate materials.

They can be classified according to their chemical structure into three families: oxygenated solvents: alcohol, ketone, etc.; hydrocarbon or hydrocarbon solvents: aliphatic, aromatic, nitrated, etc.; halogenated solvents: chlorinated, brominated, iodized, etc.

Benzene is an excellent solvent for greases, rubber and paints. It remains an essential raw material in organic synthesis. Its toxicity to the bone marrow and its carcinogenic effects have led to its use in the professional environment being severely regulated and its use restricted in cases where replacement with substitutes is impossible.

V.2.1. Benzene poisoning

Occupational poisoning has been recognized as an occupational disease since 1948. Benzene is classified as a category 1 carcinogen according to the ARC (International Agency for Research on Cancer). The term **benzolism** applies to the intoxication caused by benzene mixed with its higher counterparts (toluene, xylene, cumene) which may contain benzene in the form of impurities... On the other hand, that of benzenism refers to intoxication with benzene alone (**Figure 18**).

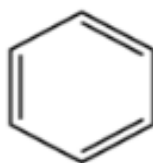


Figure.18.Chemical composition of benzene [16].

V.2.2. Use of benzene

Benzene is used in many industrial processes and is used in the composition of fuels. Household products contain almost none.

Toluene and xylene are used in many industrial processes. They are also used as solvents in glues, paints and thinners. Some people misuse glue that they inhale or sniff, or other products containing toluene, benzene or trichlorethylene. It is an addictive practice.

A. Toxicokinetics of benzene:

1. Absorption

The routes of solvent penetration are diverse.

1.1. The pulmonary route: it is the predominant route of penetration with pulmonary storage varying from 30 to 80% of the quantity inhaled.

1.2. The percutaneous route: it is far from negligible, especially when benzene comes into contact with the skin through soiled clothing or when bare hands are dipped in the solvent.

1.3. The digestive tract: it is exceptional and only concerns accidental ingestions or attempts at autolysis.

2. Distribution

Absorbed benzene is transported by the blood bound to plasma proteins and red blood cells. Due to its lipophilicity, it is quickly distributed in organs rich in lipids: liver; nervous system, bone marrow, adrenal glands. The fixation of benzene in the nervous centers is preferential in massive poisonings. In the event of chronic exposure, it will mainly be hepatic.

3. Metabolism

The metabolic transformations of benzene take place mainly in the liver but also in other tissues where it is fixed, in particular in the bone marrow. These metabolic transformations aim to make benzene more water soluble and facilitate its elimination by the kidneys. It is essentially oxidation of the benzene nucleus, which makes it more toxic in the long term.

Oxidation of benzene is carried out initially by monoamine oxygenases associated with cytochrome P-450 of the endoplasmic reticulum. It results in the formation of a very reactive, very unstable electrophilic intermediate epoxy-benzene, which can attach to cellular macromolecules (proteins, DNA) to give adducts, or lead to the formation of other metabolites: phenol, *trans*-diol-pyrocatechol, muconic acid, phenyl mercapturic acid.

The phenolic derivatives can then be transformed into conjugated sulfo and glucuronides, then eliminated through the urine. It is the in-situ formation of phenols which is responsible for the toxicity of benzene.

-The higher homologs, toluene and xylene, are oxidized directly at their side chains. They undergo only very weak hydroxylation of their aromatic nucleus and do not exhibit the hematopoietic toxicity of benzene. The specific bone marrow toxicity of benzene could be explained by the metabolic transformations carried out in the bone marrow.

4. Elimination

The most important excretion routes are:

❖ **The respiratory tracts**

It allows the elimination of unmetabolized benzene in exhaled air.

❖ **The urinary tract**

Urinary elimination of unmetabolized benzene is very low, representing less than 1%. Benzene is mainly eliminated in the form of phenols. The determination of urinary phenols is proposed as a means of controlling occupational exposure.

It is assumed that half of inhaled benzene is released with exhaled air during occupational exposure. A proportion of 30 to 40% is eliminated by the kidneys after oxidation to phenols. A small amount remains fixed at the tissue level.

V.3. Heavy metals

A metal is a chemical element, most often coming from an ore or another metal, endowed with a particular luster, a good conductor of heat and electricity, having characteristics of hardness and malleability, thus combining easily with other elements to form alloys usable in industry since antiquity.

Heavy metals are generally called natural metallic elements, metals or in certain cases metalloids (around 65 elements), characterized by a high density greater than 5g per cm³. Heavy metals are present in all compartments of the environment, but generally in very low “trace” quantities.

Classification for these different reasons, most scientists prefer to the name heavy metals, that of: “Metal trace elements” (ETM) or by extension “trace elements”.

We thus distinguish:

-Essential trace elements: these are essential trace elements for many processes Zinc (Zn), iron (Fe)...

-Non-essential trace elements: They have no known beneficial effect for the cell, but are polluting with toxic effects for living organisms even at low concentrations. This is the case for Lead (Pb), mercury (Hg)...

V.3.1. The toxicokinetics of Lead

From a chronological point of view, the most popular toxic metal was firstly lead, due to its use for drinking water pipes for millennia.

A.Absorption

Absorption of lead vapors is respiratory. Dust absorption is respiratory and digestive.

*Particles whose diameter is between 0.1 and 0.5 μm are those which are best absorbed by the respiratory route.

*Particles with a diameter greater than 5 μm are deposited in the respiratory tree, but they are drained towards the aerodigestive crossroads and finally swallowed.

B. Distribution

In a state of equilibrium, blood lead represents only 1% to 2% of the quantity present in the body. In the blood, 98% of lead is intraerythrocyte (in red blood cells). Plasma lead is partly bound to proteins.

C.Elimination

Excretion of lead is mainly urinary (> 75%) and fecal (15-20%). The rest is eliminated in the skin appendages, sweat and bronchial secretions. There is also milky excretion.

The term pesticide designates any substance or mixture used to prevent, destroy or repel organisms undesirable for agriculture or public hygiene. This is a general term encompassing a wide variety of products: herbicides, fungicide, insecticides, etc.

A pesticide can be a chemical substance, a biological agent (such as a virus or bacteria), a disinfectant or any other product that fights “pests”.

Pesticides can be classified according to their chemical families. The most important families are organophosphates, organochlorines, carbamates and triazines.

V.4. a.Organophosphates

These compounds constitute a family of pesticides acting on the acetylcholinesterase enzyme (the carbamate family also acts on this enzyme but according to a different mechanism). They operate by irreversibly blocking acetylcholinesterase, essential for nerve transfers in insects, humans, and most animals. The ability to block acetylcholinesterase

(and therefore toxicity) can vary significantly from one compound to another. For example, parathion, one of the first organophosphates, is much more potent than malathion (Mediterranean fruit fly and Nile mosquitoes) (**Figure 19**).

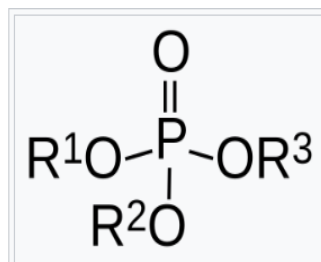


Figure.19. General chemical structure of the organophosphate functional group [17].

Organophosphate compounds are rapidly degraded by **solar radiation**, in the **air**, and in **soil**, although small amounts may persist and end up in food and water. The fact that they degrade easily makes this family an interesting alternative to persistent organochlorine pesticides. However, although organophosphates degrade more quickly, they are more toxic, which represents a risk for users of these compounds.

The most common organophosphorus compounds are: parathion, malathion, methyl parathion.....

V.4.b. Organochlorines

This family includes a large number of chemical compounds containing chlorine and some other elements. (**Figure 20**)

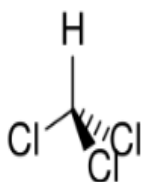


Figure.20.Representation of chloroform [18].

The most powerful and effective insecticides are organochlorines. In this family we find DDT, chlordane, and even pentachlorophenol. They are very persistent in soils, and they

also concentrate in biological tissues. Many compounds in this family are banned due to their neurotoxicity.

V.4.c.Triazines: this family covers a wide field of use. Most are used as selective herbicides. Triazines are among the oldest herbicides, with research on these compounds beginning in the 1950 (**Figure 21**).

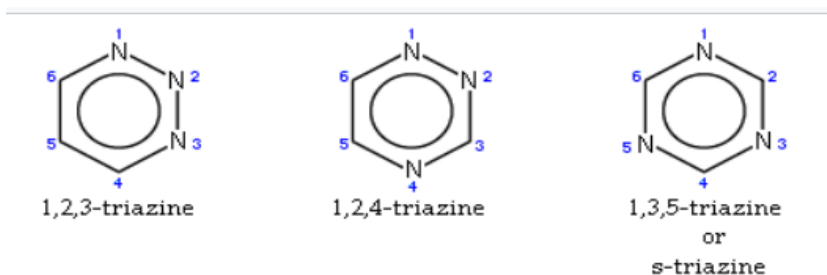


Figure .21. The three isomers of triazine, with ring numbering [19].

❖ The toxicokinetics of organophosphates

Easily absorbed through the skin and respiratory tract (aerosols) and accidentally through the digestive tract, organophosphates are distributed mainly in **fats**, the **liver** and **kidneys**, but also in the nervous system. Organophosphates are immediately active when it comes to phosphoric esters. They must first be activated into phosphoric esters when they are initially thiophosphoric esters. They are rapidly metabolized in the liver by esterases and sometimes other enzyme systems, particularly cytochrome P450 monooxygenases.

The kinetics of their absorption, distribution, biotransformations and elimination depend on the compound involved. The main urinary metabolites are **alkylphosphates** and **alkylthiophosphates**, including **dialkylphosphates**.

Most organophosphates result from the inhibition of acetylcholinesterase activity at the synapses of neurons in the nervous system.

Problems

Exercise 1

A drug with an elimination half-life of 2 hours and a distribution volume of 80 l is infused at a rate of 20 mg per hour.

- 1)- What is the plasma concentration of this drug at equilibrium?
- 2)- After how long does it take to obtain the C_{eq} ?
- 3)- What is the loading dose to administer directly IV to immediately obtain the desired C_{eq} ?

Exercise 2

After intravenous injection of 100 mg of an active ingredient having a single-compartmental distribution, the following data are available:

-distribution volume: 40 liters.

-elimination half-life: 8 hours (plasma measurements)

-in the 48 hours following the patient emitted 2500 ml of urine with a concentration of active ingredient equal to 25 mg/l, urinary excretion is considered to be total.

Calculate:

- A- The theoretical initial concentration (C_0).
- B- The elimination constant k_{el} .
- C- Total clearance of the active ingredient.

Exercise 3

After intravenous injection of a 50 mg dose of a drug into a patient, the following plasma concentrations were measured (in mg.L⁻¹) as a function of time (in hours):

Time 0: 3.45

Time 1 hour: 2.55

Time 2h: 1.65

Time 4h: 0.75

Time 8h: 0.15

- 1)-Draw the concentration curve as a function of time.
- 2)-Calculate: elimination half-life, total plasma clearance, volume of distribution.
- 3)-Calculate the infusion rate necessary to reach an equilibrium concentration of 5 mg.L⁻¹.

Exercise 4

Or a medicine presented in two pharmaceutical forms: injectable preparation (A) and tablet (B). (A) is administered by direct IV route at a dose of 350 mg.

The pharmacokinetics of the injectable form responds to a single-compartmental model and the equation which translates the variations in concentration as a function of time is of the form:

$$C(t) = 6 e^{-0.25t} \quad 6 \text{ in mg.l}^{-1}; 0.25 \text{ in h}^{-1}$$

(B) is administered orally at a dose of 500 mg. The pharmacokinetics of the compressed form responds to a single-compartmental model and the equation which translates the variations in concentration as a function of time is of the form:

$$C(t) = -5.2 e^{-1.5t} + 5 e^{-0.26t} \quad 5.2 \text{ and } 5 \text{ in mg.l}^{-1}; 1.5 \text{ and } 0.26 \text{ in h}^{-1}$$

- 1)- Calculate the plasma half-lives of the drug presented in pharmaceutical forms (A) and (B).
- 2)- Determine the absolute bioavailability of form (B).

Exercise : 5

Reminder: $\ln 2 = 0.693$.

A medicine has the following characteristics:

- elimination half-life = 6 hours.
- volume of distribution = 2 l/kg.

A 75 kg patient is injected with 500 mg of this product directly IV, then a blood sample is taken 5 minutes later once the distribution phase in the body is complete.

- 1- What will be the plasma level obtained?
- 2- What will the plasma level be 24 hours after the injection?
- 3- What is the plasma clearance of this drug?
- 4- What is the dosage to administer by continuous IV to maintain the initial rate?

Exercise 6

In an adult weighing 70 kg, a dose of 2 g of piperacillin is administered IV:

Blood samples are then taken at different times to study the kinetics plasma of this medicine (dosage: concentration of piperacillin in the blood)

T (h)	30 mn	1	2	4	5	6
C (µg/mL)	122.8	83.4	38.5	8.2	3.6	1.7

- 1- Draw the $\log C = f(t)$ curve on the semi-Log paper.

2-Comment on the curve.

3-Graphically determine $t_{1/2}$ and k_e .

4-Calculate the clearance (Cl) and Distribution Volume (Vd), interpret Vd.

The necessary formulas

Concentration at equilibrium C_{eq}

$$C_{eq} = q_0/T \times V_d \times k_{el}; q_0/T = \text{Flow (I)}; k_{el} = \ln 2/t_{1/2}$$

The loading dose

$$\text{Loading dose} = C_{eq} \times V_d$$

Volume of distribution V_d

$$V_1 = D (\text{dose})/C_0$$

Total clearance Cl

$$Cl = V_1 \times k_{el}$$

$$Cl = F \times \text{DOSE} / \text{SSC}_0 \text{ (F: bioavailability, SSC area under the curve).}$$

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