IMPORTANT

La traduction est assurée par Google traduction mais qui na pas encore

été corrigée. La version finale est cours…

KEEP IN MIND

The translation was performed by Google Translate, but it hasn't been corrected yet

We are currently working

on the final version.

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People's Democratic Republic of Algeria

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Ministry of Higher Education and Scientific Research

جامعة الإخوة منتوري قسنطينة
UNIVERSITE DES FRERES MENTOURI CONSTANTINE

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Institute of Veterinary Sciences

Department: **Animal Production**

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Teaching handout

PRINCIPLES OF PHARMACOLOGY GENERAL

Intended for 3rd year Doctor of Veterinary Medicine students

Prepared By

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Academic year 2022-2023:

PRINCIPLES OF THE PHARMACOLOGY GENERAL

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PREAMBLE

Before beginning to read this document, a few comments should be made.

decisions need to be made regarding the editorial choices adopted:

The following text is intended to be as simple as possible, so that the student, whatever
so that, with minimal effort, they can become familiar with the basics
of pharmacology. The richness of its illustrations makes it very easy to read.
Certainly, many of the concepts there are specific to the training of future
veterinarians.

With this in mind, the first chapter concerns the history of pharmacology through its early pioneers,
then returns to the teaching of the chair, here at the Institute of Sciences
The Veterinary School of El Khroub (ISVK) at the University of Constantine has been involved since
its inception. The second part is an introduction to teaching, which can only take place after some
definitions of several fundamental terms such as drug, INN (International Nonproprietary Name), MA
(Marketing Authorization), generic, and prescription. The third chapter begins with pharmacokinetics and its...
qualitative and quantitative parameters, it will be necessary to understand that this is part of the
pharmacology is inseparable from pharmacodynamics, but for pedagogical reasons, the latter study is
inevitably written in the following chapter.
Where they will discuss the mechanisms of action of the drug on the living organism, the
measurement of the dose-effect relationship, as well as some concepts of drug interactions.

Enjoy your reading!

Many thanks and tribute to

Dr. BENSEGUENI L. who has taught pharmacology

more than 20 years at ISVK,

Who had of granting us his lessons (Word, the kindness

PowerPoint) and all its documentation,

to whom we owe some parts and

from this compilation.

And

A thought for friends Ms. Leila, Pr KOHIL my K;
Pr HIRECHE S, Pr AGABOU HAS Pr DIB A, who gave
the system and a boost to This work, in record time.

With a single glance

"For the common good, you can contribute to optimizing the data in each chapter and reporting any errors that may occur; your identified suggestions will be processed to improve and enrich the information in this course. We are always listening."

SUMMARY

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LIST OF ABBREVIATIONS

PA: Active ingredient.

IUPAC: International Union of Pure and Applied Chemistry.

WHO: World Health Organization.

INN: International Nonproprietary Name.

ND: Registered name.

UPSA: Union of Applied Scientific Pharmacology.

AMM: Marketing Authorization.

DMV: Dictionary of veterinary medicines.

ATC: Anatomical, therapeutic, chemical.

ATCvet: Anatomical, therapeutic, chemical veterinary version.

RCP: Summary of Product Characteristics.

pH: potential of hydrogen.

AUC: Area under curve.

Tmax: Maximum time.

Cmax: Maximum concentration.

F: Bioavailability.

IV: Intravenous.

SC: Subcutaneous.

IM: Intramuscular.

IP: Intraperitoneal.

LP: Extended Release.

CNS: Central nervous system.

Vd: Distribution volume.

M: Medicine.

Cm : Plasma concentration.

NADPH: Nicotinamide adenine dinucleotide hydrogen phosphate.

FAD: Flavin adenine dinucleotide.

NOR: Nitrogen Ohne Radical.

MAO: Monoamine oxidase.

DAO: Diamine oxidases.

PAPS: Phosphoadenosine phosphosulfate.

CN: Cyanide.

CYP: Cytochrome P450.

Cl: Clearance.

Q: Blood flow.

E: Extraction coefficient.

CA: Concentration of the drug at the entry of the organ.

LIST OF ABBREVIATIONS

CV: Drug concentration at the organ exit point.

T½: Half-life time.

GDP: Guanosine diphosphate.

GTP: Guanosine triphosphate.

ATP: Adenosine triphosphate.

cAMP: Cyclic adenosine monophosphate.

IP3: Inositol triphosphate.

DE50: effective dose 50.

Emax: Maximum effect.

AE: Full agonist.

LD50: Lethal dose 50.

Glossaire	Glossary
Absorption	Absorption
Adjuvant	Adjuvant
Autorisation de mise sur le marché	Marketing Authorization
Biodisponibilité	Biodiscability
Bolus	Bolus
Capsule	Capsule
Diagnostique	Diagnostic
Distribution	Distribution
Efficacité	Efficience
Elimination	Elimination
Excipient	Excipient
Gélule	Capsule
Indication	Indication
Intraveineuse	Intervenus
Médicament	Drug
Métabolisme	Metabolism
Notice	Package Leaflet
Ordonnance	Prescription
Pharmacologie	Pharmacology
Pharmacocinétique	Pharmacokinetics
Pharmacodynamie	Pharmacodynamics
Posologie	Dosage
Principe actif	Active Ingredient
Pronostic	Prognosis
Puissance	Power
Récepteur	Receptor
Solution	Solution
Sirop	Syrup
Traitement	Treatment

INTRODUCTION GENERAL

Pharmacology is a vast discipline that covers the study of drugs from their development to their use after they are marketed. However, it also includes, among other things, the study of the interactions of chemical substances with all living organisms.
from its administration until its elimination.

From this representation, everything that the body does to the drug is considered Pharmacokinetics, on the other hand, which studies everything a drug does to the body, is the branch that studies pharmacodynamics. Ultimately, pharmacokinetics is the study of the phenomena that concern the **fate of the** drug substance in
the body and which will determine the **concentration** of the substance in the compartment where it is active and the evolution of this concentration **over time** .

Pharmacodynamics is the detailed study and evaluation of **cellular response ;** the activity of a drug active ingredient on a **living organism ;** a
healthy, normal tissue. It deals with the interaction between the pharmaceutical product (PA: chemical substance possessing a **pharmacological effect)** and **its target** (receptor,
free protein, ion channel) .

Printed and electronic media each have their advantages and disadvantages. We can, after all, print computer files, and we do so quite often. Electronic media is more flexible and, above all, easier to update regularly.
However, for in-depth work, traditional writing remains entirely relevant. It allows for erasures, additions, highlighting, and comments.

This handout, " Principles of There General Pharmacology », proposes a compilation of theoretical courses from the first part of the chair of pharmacology, intended for the use of third year Veterinary Sciences students, in accordance with the program of the national pedagogical council.

Considering the following aspects of the veterinarian's future activity:
Firstly, as an **animal doctor,** the veterinarian must possess the
means of choosing one's therapy by knowing the medications adapted to the case
to deal not only with matters relating to their activity

(indication, knowledge of usage rules) but also with regard to their toxicity to different animal species

It is also this second aspect— **the pro-pharmacist veterinarian—** that this pharmacy education must prepare for. Veterinarians not only have the possibility of prescribing treatments for animals after establishing the diagnosis of the disease they have, but they can also dispense medication necessary for treatment.

Therefore, their activity with animals is analogous to that of doctors and... pharmacists for both men and women.

Finally, the **veterinary hygienist** must ensure that the foodstuffs of origin Animal products (meat, milk, eggs, fish, honey) do not contain drug residues veterinarians, which may pose a danger to consumer health. For this reason, it will have to ensure the correct use of the veterinary medicinal product and in particular the compliance with the " **withdrawal period** " by carrying out residue analyses on these foodstuffs food

However, medication and its proper use constitute a major health issue. Public. Thus, pharmacology is the discipline that deals with any substance of animal or plant origin introduced into a living organism, with the aim of treating, preventing, correcting, and/or diagnosing a pathology. It studies the fate of the active ingredient, its effects, and its mechanisms of action with the receptors of the target tissue.

CHAPTER I

TEACHING OF THE PHARMACOLOGY

GOALS :

- Distinguish between pharmacology and pharmacy
- To know the origin and history of pharmacy
- To know the chair of teaching at the institute
- Be familiar with the pharmacology unit's program

I.1. PHARMA/CO/or/MACIE

I.1.1. PHARMACO (meaning remedy)

Pharmacology is the study of medicines in the strictest sense of the term.

It is a scientific discipline focused on living organisms, a subdivision of **biology.**

It is the science that studies the **interactions** between an **active molecule** and **a living organism.** in which it evolves. (Figure 1)

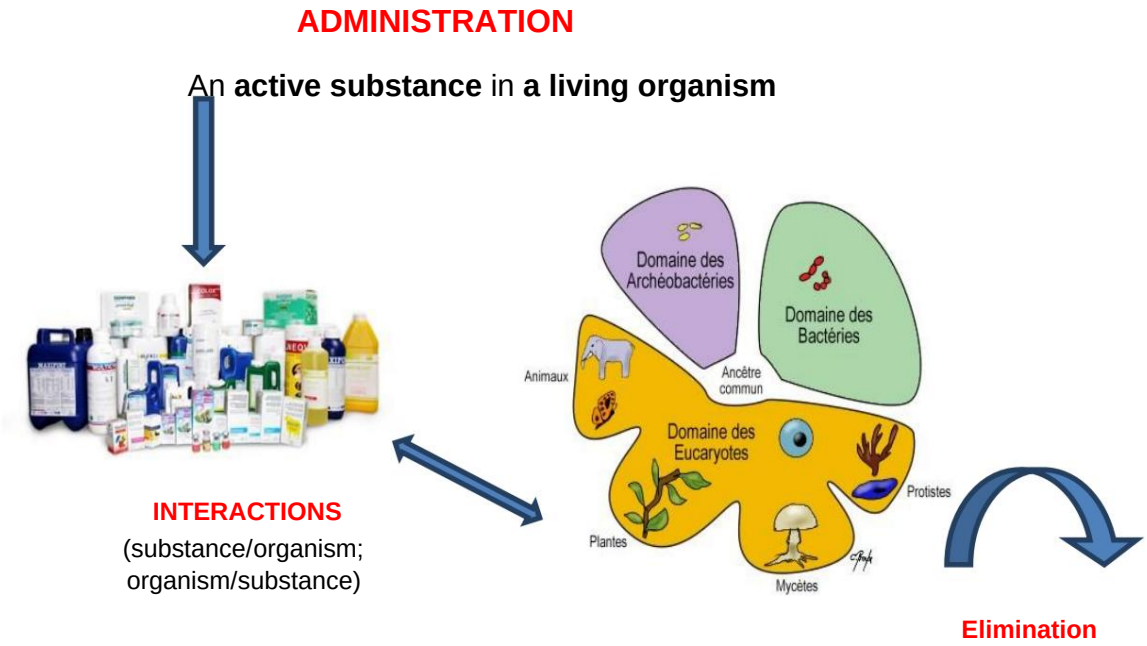


Figure 01: Illustration of the definition of pharmacology (Personal)

This definition covers an extremely broad field since it includes, in addition to pharmacokinetics, pharmacodynamics, pharmacovigilance and drug dependence, the study of drugs in animals (pharmacology).

experimental), or in humans (clinical pharmacology).

Molecular pharmacology studies the physicochemical properties of drugs and their relationship to their biological activity.

The study of drug use, its context, and its consequences for society is the subject of pharmacoepidemiology, pharmacoeconomics and social pharmacology.

From an academic perspective, there are several areas of focus:

- **General pharmacology** is the study of the basic principles of absorption, of the distribution, molecular mode of action and elimination of substances active;
- **The pharmacology of specialties,** which covers the analysis of the functional and therapeutic aspects of the different classes of drugs in relation to with the major functions of the organism; and
- **the treatment of specific diseases**

I.1.2. PHARMA/CIE

It is the set of theoretical and applied sciences that lead to the **design, to manufacture, control** and **dispense medicines "** (National Academy of pharmacy 1997).

This dispensing takes into account possible drug interactions between the It can detect chemical molecules or interactions with edible products. It also allows for the verification of doses and/or potential contraindications.

The term pharmacy It also refers to a **pharmacy,** that is, a place intended for **the storage** and **dispensing of medicine.** This place is under the responsibility of a pharmacist who can **prepare compounded medications** prescribed by a doctor for a specific patient and supervise the work of pharmacy technicians

I.2. MEDICINE IN ALGERIA

Throughout its medieval history (in the Middle Ages) and due to its geographical position between East and West, Algeria benefited from a continuous cultural and commercial movement, giving rise to numerous centers of civilization in **Tlemcen, Bejaia,** Oran, Tahert, Algiers, Annaba, Constantine, Cherchell, Ténés, Mostaghanem, where Scholars and students went in search of Science.

We quote, ASSEM ESSADRATI, **IBN EL BOUTHOUH,** IBN ABI EL MALIH…

Like other Islamic cities, such as **Cordoba, Seville, Fez, and Marrakech, Kairouan, Tunis, Cairo, Baghdad, Damascus, Ray,** a social welfare system was established there organized within an urban complex including hospitals, schools where Grand masters provided their courses, public baths, mosques, schools of theoretical instruction, libraries and caravanserais.

At the time when the scientific level was beginning to decline in Andalusia and in In the East, medieval North Africa maintained the torch of cultural influence.

- Algerian medicine during the Ottoman period was of a naturalistic type and relied on diet, medicinal plants, cures…The country had good doctors who knew how to take care of all types of fractures, who treated wounds properly, operated on cataracts, and even performed trepanations.

  Admittedly, there was no centralized healthcare management organization, even though the profession was regulated and administered by an elected union.

- The following are cited: MOHAMMED EL KÉBIR, SAID IBN AHMED EL MOKRI, ECHAFFII EL MAKKY, ABDERREZAK IBN HAMADOUCHE EL JAZAIRI

It is, moreover, difficult to speak of the supremacy of European medicine at that time, because major discoveries, particularly those relating to the identification of microbes responsible for major, disruptive epidemics, had only just begun to be made. recorded only towards the end of the 19th century!

The most remarkable aspect of healthcare policy in Algeria at that time was its humanitarian character. Several facts demonstrate this, notably the hospital charter signed in 1693 by Dey Chaban, which imposed a tax on all goods. landed at the port of Algiers. This tax was used exclusively to finance the hospitals in Algeria to take care of the sick.

I.3. HISTORY OF PHARMACY

There is no certainty about its origins. The disease being as vigilant as humanity, in From the earliest times, man has always tried to care for his fellow man. The first healers were sorcerers, priests.

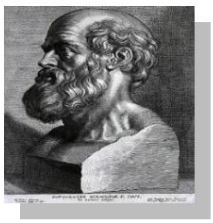
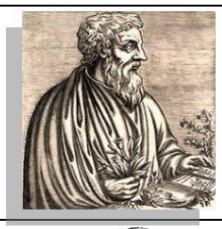
The drug's action on the body was not recognized as the factor in the cure.

Indeed, for centuries, medicine and pharmacy were confused and practiced by the same person (examined the patients, prescribed the medications, carried out their preparation and delivery to patients).

The genesis and history of pharmacology can be subdivided into:

- The development of chemical pharmacy (Table I),
- The flourishing of research in the 20th century,
- The need for teamwork (chemists, bacteriologists, physiologists, clinicians) is increasingly being felt and is becoming the mandatory condition of discovery of new drugs.
- Pharmaceutical research continues to create new therapeutic substances, suggesting that one day we may be able to control some of the ailments associated with... Aging, cancer, AIDS…

Table I: Pioneers of pharmacology (Benyousseef, et al 2016)

	**HIPPOCRATES,** nicknamed the father of medicine born around 460 BC on the island of Kos and died in 377 av.
	**Dioscorides,** Greek military physician born between the years 20 and 40 AD, in Anazarbus and died around 90 AD.
	**GALIEN,** the father of pharmacy born in Pergamon in Asia Minor in 129 and died around 216
	**IBN JAZZAR** born in 878 in Kairouan and died in the 980s in _____ Kairouan was a physician from Ifriqiya (modern-day Tunisia) who lived in the 9th century. and X^e centuries

I.4. ALTERNATIVE MEDICINES

- **Phytotherapy:** medicine based on the use of plants and extracts of plants for curative but also preventive purposes.
- **Aromatherapy:** this medical technique uses essential oils obtained by distillation of various aromatic plants such as thyme, Lavender. These oils are complex products that are often used through the skin.

I.4.1. IMPORTANCE OF MEDICINAL PLANTS

Medicinal plants are important for pharmacological research and In the development of medicines, approximately 80% of the world's population relies exclusively on medicinal plants for treatment.

In Europe, 35% of medicines prescribed by doctors are of natural origin. More than 50% of over-the-counter medicines are plant-based.
medicinal

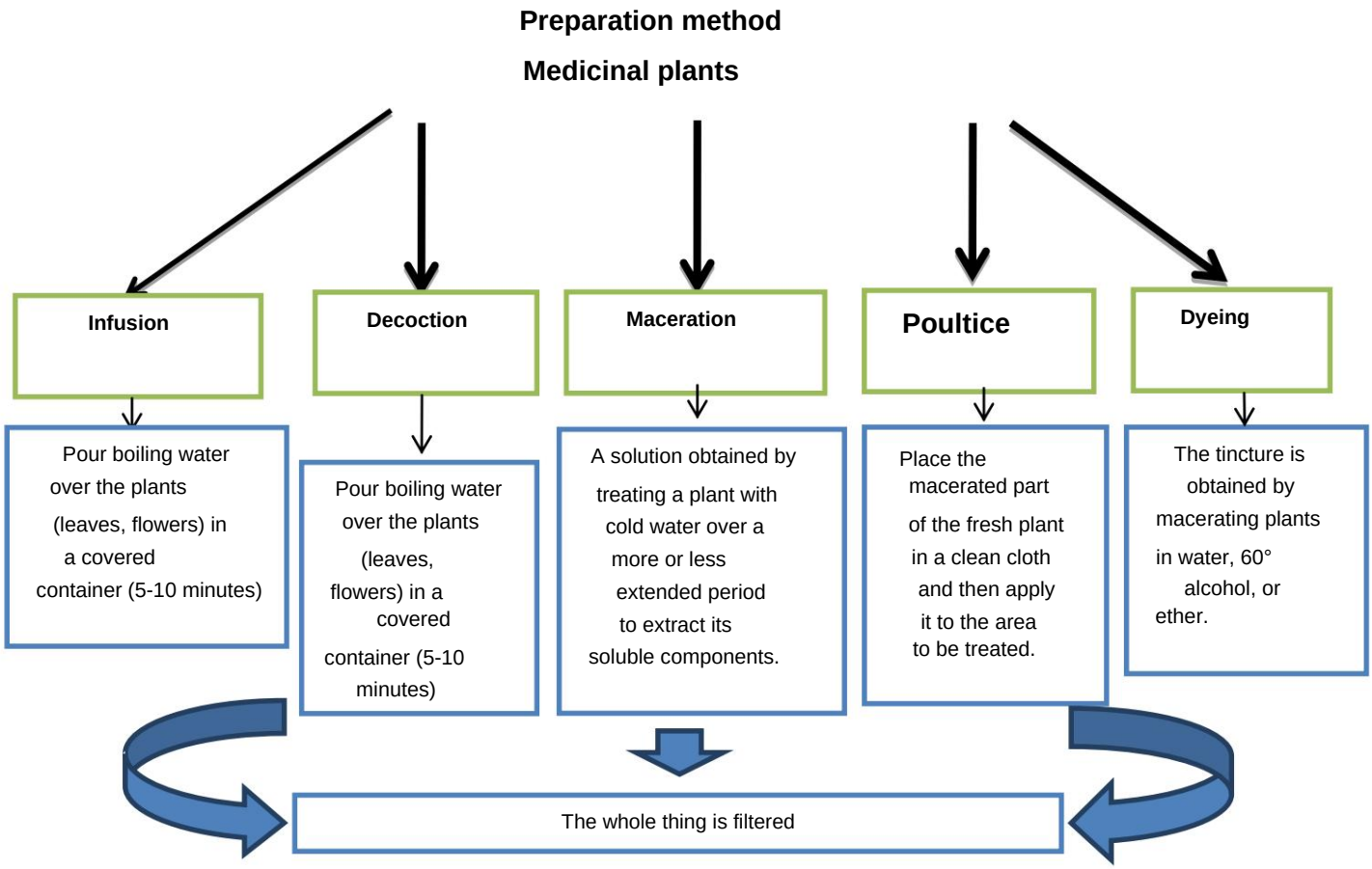


Figure 02: Method of preparing medicinal plants (Torche S, 2015)

I.4.2. WILLOW BARK IN HISTORY

- Hippocrates (5th century BC) **against the childbirth pains**
- Galen (2nd century AD) describes the properties **antipyretic and anti-inflammatory properties** of the leaves of willow.
- Widely used in the Middle Ages against fever and pain

Detailed description of the analgesic, antipyretic and anti-inflammatory effects of willow bark (Salix alba) in **1763**

- Isolation of salicin in **1829 (_ Salix alba L.)**
- Around **1840,** salicylic acid was obtained by chemical oxidation of salicin
- The discovery of salicylic acid in **1875**

This step was followed by the synthesis of acetylsalicylic acid or **aspirin.**

in 1895, as NSAIDs

- Salicylic acid is the precursor to aspirin.

I.5. PHARMACOLOGY AT THE EL KHROUB INSTITUTE

I.5.1. TEACHER INTERVENTION

- Strangers (1975)
- Dr. MEGUNANI (1982)
- Dr BENSEGUENI Lynda (1986-2014) and Pr HAMDI PACHA Youcef (1990-2017)
- Dr BENSEGUENI Lynda Dr BEROUAL K (2008-2013) and Dr TORCHE (2013-2014)
- Other assistants: (2006-2010)
- Currently: Dr. BEROUAL and Dr. TORCHE (2015-2023).

I.5.2. THEORETICAL PROGRAMME

- **GENERAL PHARMACOLOGY**

  Introduction to Pharmacology

  Pharmaceutical forms Administrative channels

  Pharmacokinetics Pharmacodynamics

- **SPECIAL PHARMACOLOGY**

  Medications by group (antibiotics, anti-inflammatories, antiseptics)

  antiparasitics)

  Medications for major bodily functions (respiratory, digestive, urinary disorders)

I.5.3. PRACTICAL PROGRAMME

- Presentation and identification of commonly used medicines
- Forms and medicinal products for veterinary use
- Parenteral routes of administration
  - Farm animals
  - Laboratory animals
- Administration channels in situ
- Preparation of antiseptic

CHAPTER II:

INTRODUCTION TO THE PHARMACOLOGY

GOALS

By the end of this chapter, the student will be able to:

• Know how to define some concepts: Pharmacology, Drug, Pharmacodynamics, Pharmacokinetics, Pharmacognosy, Medical prescription. •

Understanding the origins of medications

• Identify the role of the different components of a medicine

• Identify the criteria that a drug must meet

• Identify any medication by its packaging (box) and/or (Note)

II.1. DEFINITIONS

II.1.1. PHARMACOLOGY

Pharmacology (pharmacology) : IVent of the Greek word " Pharmakon " which means remedy but also poison .

It is defined as " a scientific discipline that deals with the source of the physical and chemical properties, biochemical and physiological effects, mechanisms of action and therapeutic uses of drugs".

To achieve this, pharmacology integrates fundamental concepts and basic data from physiology, pathophysiology, biochemistry, genetics and molecular biology , but also from **medical sciences** (pathology, clinical practice, toxicology) and **pharmaceuticals** (preparation, dispensing). This is the “Crossroads” Science.

II.1.2. MEDICINE

Medicine: in Latin. Medicamentum: Drug

In Algeria, medicine is defined by Law No. 85-05 of February 16, 1985, concerning the protection and promotion of health. Article 170 defines a medicine as “any substance or composition presented as possessing the properties curative or preventive with regard to human or animal diseases, all products that can be administered to humans or animals for the purpose of establishing a medical diagnosis or to restore, correct, modify their organic functions.”

II.1.3. PHARMACY

This is the place where pharmaceutical products are sold or marketed.
(drugs).

II.1.4. PHARMACOGNOSIS OR MEDICAL MATERIAL

Science deals with the natural origin (plant, animal, mineral) of
Active ingredients.

II.1.5. PHARMACEUTICAL CHEMISTRY

This is the science that deals with the relationships between the structure of chemical substances and their therapeutic properties.

II.1.6. GALENIC PHARMACY (LA GALENIC)

This is the science that deals with the preparation, presentation, and preservation of pharmaceutical products, in the form of medicines, sold in
pharmacies ready for use and subject to regulations.

II.1.7. PHARMACOKINETICS

It studies the different phases of the molecule's (drug's) fate in the body: absorption, distribution, biotransformation and elimination.

II.1.8. PHARMACODYNAMICS

It deals with the mechanisms of action of drugs and their biochemical effects.
and physiological effects on the living organism.

II.1.9. CLINICAL PHARMACOLOGY

It deals with the effects observed directly on the general state of the human organism and animal.

II.1.10. PHARMACOGILANCE

Pharmacovigilance refers to all the techniques for identifying, evaluating and preventing the risk of adverse drug effects.
walk.

II.1.11. XENOBIOTIC

Xenobiotic (xeno = foreign, bio = living organism): any substance foreign to a living organism and naturally present in trace amounts (small quantities). But which accumulation is sometimes toxic.

Toxic (or poison)

Said of a dangerous substance that causes the body to enter a morbid state. or to death, e.g., Rodenticide poisoning "rat poison".

II.1.12. TOXICOLOGY

This is the science that deals with the harmful effects on the human or animal organism of a biological, chemical or drug product, which are classified as "Toxic".

Noticed: The lines between medicine and toxin are very difficult to establish; it is primarily a The question of dosage, which itself depends on various factors (age, combinations of medications, variations in the body's sensitivity to medications).

The toxicity of a drug is determined by its dose: "The dose makes the poison."

II.2. MEDICINE

II.2.1. ORIGIN

It is referred to as drugs Natural products are used as they exist for their therapeutic properties or from which it is possible to extract medicines. Medicines can be of various origins. Drug miscellaneous:

II.2.1.1. NATURAL

Drugs belong to three kingdoms: plant, animal, and mineral.

• **Herbal medicine:** The use of plants in therapy (phytotherapy) is very ancient and is currently experiencing a resurgence of interest. It is possible to use whole plants (herbal teas) or their extracted products.

They provide (essential oils). Many active ingredients used in therapy are extracted from plants: alkaloids (quinine, morphine), heterosides (digitaline).

• **Animal-derived medicinal products:** Human blood and plasma, therapeutic sera human or animal active ingredients obtained by extraction (hormones and enzymes)

essentially): Insulin (an antidiabetic hormone extracted from the pancreas), Heparin: anticoagulant medication extracted from the lungs.

• **Mineral-based medicinal product :** Used as active ingredients or excipients: water, clays, calcium bicarbonate , iodine, silver, Na+ chloride .

II.2.1.2. SYNTHETIC OR ARTIFICIAL

Many drugs are obtained by synthesis; they have the same effect as the natural molecule when binding to specific receptors, e.g., Sulfonamides, Chloramphenicol.

II.2.1.3. SEMI-ARTIFICIAL OR SEMI-SYNTHETIC

An inactive natural substance can be modified in the laboratory and transformed into a medicinal product whose assembly and modification will be ensured by means chemicals.

This is how a series of semi-synthetic penicillins were obtained from of 6-aminopenicillinic acid, itself removed from cultures of penicillium ·

II.2.2. STANDARD COMPOSITION

The drug can be simple (consisting of a single element) or compound (consisting of several elements).

II.2.2.1. ACTIVE INGREDIENT (PA)

A medicine acts through one or more constituents called active ingredients.

The active pharmaceutical ingredient (API) is the parent molecule (or base) of the drug intended for action. desired pharmacological effect. This is the part of the drug that gives it its properties. curative or preventive.

The active substance is the only main fundamental component (mandatory)

II.2.2.2. ADJUVANT

Adjuvant (Add) or Auxiliary (Accompany):

This is the molecule that adds its action to the active ingredient to contribute to a For the best pharmacological effect, this molecule must be specified in parallel with the PA.

Example: Local anesthetic + Vasoconstrictor.

Generally, the active ingredient(s) are associated with an excipient(s) or vehicle(s).

II.2.2.3. EXCIPIENT OR VEHICLE

Excipient: in Latin Excipio = To receive (that which receives the molecule)

Vehicle: that which transports the molecule to its point of absorption

An excipient is a substance (in sufficient quantity) without action pharmacological in order to give the molecule an appropriate pharmaceutical (medicinal) form and must provide with it a perfectly homogeneous.

In addition to its galenic role, the ideal excipient must be chemically stable, non-reactive with respect to the active substance and other excipients, inert with respect to the human or animal body, and finally, well-characterized to be accepted by industry and the regulatory bodies.

The excipient must always be compatible with the active ingredient, and it must not cause noticeable (obvious) effects, e.g., allergic reactions or intolerance in people intolerant to the active ingredient. lactose.

It must release the active ingredient quickly if a fast action is desired, or slowly if... looking for delayed action

The excipient is always expressed in the composition of the medicine as QSP: quantity sufficient to (form and convey) one unit of the active ingredient (ml or mg or IU).

However, it remains a secondary and optional element in the composition of the drug.

II.2.2.4. CONCEPT OF PLACEBO

This is a term given to any preparation devoid of PA (active ingredient).

A placebo contains only the excipient and has the same form as the medication. Placebos are used primarily for their psychological effect, known as the "placebo effect." They have no real pharmacological effect.

During clinical trials for the development of future drugs, the placebo is used as a "Control", to verify that the excipient does not influence the results of the experiment.

II.2.2.5. OTHER ELEMENTS WITH SECONDARY ACTION

Excipients are classified according to their function as follows:

ÿ **Interludes (Intermediate)**

Chemical elements that facilitate the homogeneity of complex drugs, when two or three molecules of the composition are chemically dissociable, this is the case for creams and ointments for example.

ÿ **Corrective agents (sweeteners)**

Elements that are added with the aim of correcting: taste, smell, making a preparation intended for oral use pleasant and/or masking the bad taste of an active ingredient.

ÿ **Dyes**

Colored substances used as a homogeneity indicator for a mixture of powders or to identify the finished product.

ÿ **Aggregates**

Excipients that ensure the cohesion of a powder mixture and allow the tablet manufacturing.

ÿ **Preservatives**

Substances intended to prevent chemical degradation or alteration microbiological of a drug.

*** In fact, another factor also comes into play from a pharmaceutical point of view: **packaging, which** is an element of protection, presentation, and identification of a form medicinal. This plays a major role, primarily for preservation and employment.

Therefore, the pharmaceutical definition of a drug is based on the triad: principle active ingredient and excipient in a certain form, packaging.

II.2.3. NAME

Every medicine is presented under a special name. It has a name chemical, an international common name and a specialty name.

II.2.3.1.SCIENTIFIC NAME

It corresponds to the chemical nomenclature (chemical name) of the compound. It is developed taking into account the very strict nomenclature rules established by the IUPAC. (International Union of Pure and Applied Chemistry). It has the advantage of being unambiguous, but with the disadvantage of being complicated, long to write and read, and difficult to retain.

Example:

- ÿ Acetyl Salicylic Acid
- ÿ Sodium 3,3-dimethyl 7-oxo 6 ÿ phenylacetamido 4-thia-azabicyclo 3,2 heptane 2 carbocyclate

II.2.3.2. INTERNATIONAL COMMON NAME (INN)

It corresponds to the name given to the parent molecule, a simple, practical name Its use and usability worldwide are supported by the WHO (Organization World of Health).

Example:

- ÿ ASPIRIN is the INN for Acetyl Salicylic Acid.
- ÿ Penicilline is the INN of Sodium 3,3-dimethyl 7-oxo 6 phenylacetamido 4 - thia-azabicyclo 3,2 heptanes 2 carbocyclate

The DCI is therefore often preferred. More condensed, it is inspired by the structure chemical structure of the molecule.

It is constructed from key segments that are either prefixes or Suffixes allow us to place a chemical substance in a pharmacological class.

The main key segments are listed in the following table

Table II: Main segments for ICD and their meanings (Kopp-Kubel, 1995, Ben

(Youssef et al., 2015)

Syllable	Pharmacological Significance	Example From DCI
André Or Stan	Androgenic steroids	Androstanolone Stanozolol
arol	Coumarin-derived anticoagulant	Acenocoumarol
caine	Local anesthetics	Lidocaine
cef	Antibiotics possessing a cephalosporan acid core	Cefaloridine
cillin	Antibiotics possessing a nucleus derived from amino-6 acid penicillanic	Cloxacillin
cycline	Tetracycline-derived antibiotics	Doxycycline
East	Estrogens	Benzestrol
gesture	Progestin steroids	Norgestrel
ium	Quaternary ammonium compounds	Benzalkonium
Sulfa	Antibacterial sulfonamides	Sulfadiazine

II.2.3.3.SPECIAL NAME

It is chosen and registered by the manufacturer to market its
The drug is the brand name or the registered trademark (RN).
Example: ASPEGIQUE® ,ASPIRIN 500® , CATALGINE® : These are registered trademarks of ASPIRIN.

AMOXIL, CLAMOXYL, EXTENCILLINE, ORACILLINE: these are examples of non-drugs (NDs) from the PENICILLIN

The special designation is followed by ND or an asterisk: “*” or “ ® ”
Registered (This is a protected, officially registered trademark: no other
The manufacturer does not have the right to copy it unless they change one or more letters.
It is protected by trademark law. No rules govern its
choice.

The names of specialties are generally easier to remember. In this
In this field, imagination reigns supreme, and the creation of a brand name refers only to the commercial imperatives.

Many registered trademarks can refer to the same active ingredient.
medicinal product when its exploitation is no longer under patent and falls into the public domain. This special designation is established:

ÿ either by imagining a fanciful name that might evoke the therapeutic action,
the origin of the active ingredient, the name of the laboratory
ÿ either by associating the scientific or common name with the name of the laboratory
manufacturer.

Examples: CHIBRET atropine eye drops, UPSA aspirin

Example of names for the same drug (Active Ingredient):

Scientific name	(Dimethyl amino-3 propyl)-10 phenothiazinyl-3)-1 ethanone-1
Common name	Acepromazine
Special designation	CALMIVET®, VETRANQUIL®

Noticed : The special designation includes two names:

ÿ **Princeps :** this is the brand name of the drug given by the laboratory that designed it ("to and made (Princeps: of ("first") and who is the capio take"), etymologically: that first to take the initiative.

ÿ **Generic :** this is the trade name given to the different copies of a drug originals manufactured in laboratories other than the original laboratory, after the period exclusiIV (expiration of the first laboratory's patent).

Example : DCI: Loratadine / Princeps: Clarityne / Generic: Akarid

What is a generic drug?

When a pharmaceutical company develops a new drug, it receives a patent for that original drug. This patent allows it to be the only one authorized to sell it.
to put this drug on the market.

After the end of the exclusivity period for the original drug, other companies may produce a copy of this drug (same INN), giving it another name often based on the scientific name of its active substance.

Generic drugs require marketing authorization (MA), but the application process is less complex (simpler) because the studies have already been carried out by the manufacturer of the original drug.
(original specialties). But the generic must prove the bioequivalence (same action) of its product (copy) compared to the original (original molecule).

A generic drug therefore refers to the notion of a product "essentially similar to a drug already on the market.

It is therefore an "exact" copy of a reference or original drug. It has the same pharmaceutical form and therefore the same qualitative and quantitative composition.
that of his area of expertise.
Generic drugs are subject to the same safety and efficacy standards as reference drugs.

The price difference between a brand-name drug and a generic is around 30 to 60%.

The manufacturer of these generics has virtually no investment to make for the research and development and marketing.
A generic drug is cheaper than the original drug because it does not require a basic research program; indeed, the molecule(s) that make it up are already available.
compose(s) a/ont already been studied.

Three types of generic drugs

- **The copy-copy :** an exact copy of the original medicine: same substance active ingredient, same quantity, same dosage form, same excipients. These generics are often produced by the laboratory that produces the similar original product.
- **Similar medications :** the generic differs from the original brand-name drug in its use of a different excipient. But neither its pharmaceutical form, nor its quantity, nor its active substance do not change
- **Assimilable medications :** modifications compared to the original concern both the pharmaceutical form and the chemical form of the active substance

These drugs must also prove their bioequivalence

II.2.4. CATEGORIES

There are many different ways to classify medications. They can be
Arranged according to their preparation methods, we can distinguish:

A) Medicinal products prepared extemporaneously

They are prepared on request, upon presentation of a prescription, or at
At the moment, their use by the practitioner is determined. Two main categories are distinguished:

- ÿ **Over-the-counter medications**
- ÿ **Compounded medications**

B) Pre-prepared medications

II.2.4.1. OFFICIAL MEDICINES

Their composition is perfectly codified in an official work, the
The National Formulary or "codex", a supplement to the French Pharmacopoeia, does not describing the raw materials.

A doctor or veterinarian prescribing an over-the-counter medication is not required to specify its composition. For the prescription to be filled, it is sufficient to add the
the term "officinal" in the name of the medicinal product as it appears in the Formulary National.

Example The official zinc oxide ointment contains the following ingredients, as required by law :

- ÿ Zinc oxide: 10 grams
- ÿ Vaseline oil: 10 grams

Vaseline: 80 grams

The pharmacist will find all the necessary information in the National Formulary.
It is not necessary to indicate the composition of this ointment on the prescription.

In case the prescriber had written (worded) their prescription in such a way that
Although several preparations may correspond to this one, the pharmacist executing the prescription will always choose to make the least active of them.

II.2.4.2. COMPOSITED MEDICINES

The composition of which is chosen by the veterinarian. Their formulation addresses the need to better tailor the therapy to the sick animal, which benefits from a medication "on-site." measure ".

Example :

ÿ Mercuric iodide: 5 grams

ÿ Lanolin: 95 grams

The practitioner therefore assumes full responsibility for the effectiveness and harmfulness. These formulations must take into account incompatibilities and strive to find associations with a potentiated effect.

II.2.4.3. MEDICINE PREPARED IN ADVANCE

A century ago, official and compounded medicines represented almost all of the available medications. all the medications used. They have been gradually replaced by medications prepared in advance.

Initially, many pharmacists prepared some formulas (syrups, potions, ointments) and sold them in their pharmacy and at a certain a number of colleagues under the name "Homemade Products".

Next, establishments specializing in the preparation of medicines have They were developed and marketed throughout the country and abroad. Pre-prepared medicines, used without processing and given a special designation, i.e., a brand name or registered name, are called "Specialties" Pharmaceuticals".

Veterinary medicine has undergone a similar evolution. Compound and extemporaneous medicines have been progressively replaced by pharmaceutical specialties, which now represent almost the entire market.
The new development is its increasing use, especially in large workforces. Animal feed, or "medicated feed," greatly facilitates the administration of medication to animals. Medicated feed is prepared from special premixes known as "premixes for medicated feed."

ÿ **Medicated foods**

It is important to clearly distinguish

here: • On the one hand, the manufacture of a medicated food, which is food obtained by Incorporation of a premixed medicinal product: this corresponds to an activity of of medicinal nature.

On the other hand, the prescription of a specialty in the form of an oral powder, which must be incorporated by the farmer into the feed at the time of their distribution to his animals and immediately consumed: there is no official act here. In particular, with the aim of preserving the medication.

II.2.5. PHARMACEUTICAL CLASSIFICATION

Drug classes can be defined in different ways.

Drug classification takes into account the therapeutic classes of the main pharmacological functions (grouped into pharmacological classes) and the chemical structures of the active ingredient, designated by their INN.

Drugs are classified according to two types of properties (which are closely related): therapeutic properties and pharmacological properties; therefore, we will speak of therapeutic classes and pharmacological classes. This is how it will be done. in this course.

ÿ **Therapeutic classes**

It is a classification system designed according to the pathology being treated. The therapeutic classes are presented in the Vidal or the Therapeutic Dictionary (in human medicine) and the DMV or the DMVM (in veterinary medicine).

ÿ **Pharmacological classes**

=> Within each therapeutic class there are several "Classes" pharmacological" (the action of the active ingredient on the body),

Example 1: Within the therapeutic class of "Anti-infectives", we distinguish the classes The following pharmacological agents: Antibiotics, Antiseptics, Antiparasitics, Antifungals, Antivirals.

=> Within each pharmacological class there are several "Categories pharmacological"

Example 2: within the pharmacological class of antibacterials or antibiotics, the following pharmacological categories are distinguished: Beta-lactams, Macrolides, Tetracyclines.

=> Within each pharmacological category, there are several **"Groups"**
pharmacological"

Example 3Within the pharmacological category of Beta-lactams, we distinguish the
The following pharmacological groups: Penicillins and Cephalosporins.

*** Due to the complexity of drug classification, drugs are grouped into "therapeutic classes" or "therapeutic families" or **"pharmacotherapeutic classes"**

Generally speaking, medications are either specific to a single family therapeutic either concern a few therapeutic families (this is the case of ASPIRIN).

Note : The **ATC (Anatomical, Therapeutic, Chemical)** classification system has was designed in the 1970s and then recommended as an international standard by the WHO in 1996. It is an inventory system for preparations for therapeutic use to which assigned a **code** that can be used for their classification.

It is a didactic and administrative tool for grouping medications by class. depending on their therapeutic category. The veterinary version of the ATC system, **ATCvet,** is based on the same principles as the ATC system for human medicines. It was developed in a harmonized manner from 1990 onwards, then recognized and supported by the WHO as a standard international from 2001.

II.3. PRESCRIPTION AND DISPENSING OF THE MEDICINE

II.3.1. MARKETING AUTHORISATION: AMM

It is an administrative permission (approval) (national or European) issued to a holder responsible for placing a medicinal product on the market after evaluation of the quality, safety and effectiveness of the specialty concerned.
It can also be withdrawn or suspended by the administration according to the procedures laid down by regulation.

ÿ **Application for marketing authorization**

The marketing authorization application submitted by the pharmaceutical company must include a great deal of information about the drug and includes essentially 3 parts:

1. Analytical expertise: physico-chemical characteristics (expertise on formulation, manufacturing processes, raw material control protocol, stability and shelf life)

2. Pharmacotoxicological expertise: animal studies

3. Clinical expertise: Phase I, II, III and IV human studies (Huriet-Serusclat Law (88.1138 of 20/12/1988) regulates the conduct of clinical trials in order to to protect individuals participating in biomedical research and to guarantee rigor Scientific trials table. II)). The purpose of clinical expertise is to put in evidence of the activity and adverse effects of a drug.

Table III: Clinical expertise for obtaining MA (Jorgensen, 2017)

Clinical expertise for obtaining a marketing authorization			
Final Phase		**Population** **Number of subjects**	**Aim**
I	Toxicity	Healthy volunteers (a few dozen)	Determining a **toxic dose** (identifying the profile) of the molecule) Pharmacokinetics.
II	Activity	Healthy volunteers, patients (dozens, even hundreds)	Finding the **effective dose** Pharmacodynamics
III	Efficiency	Patients (hundreds, thousands): homogeneous groups	Demonstrations of therapeutic efficacy (comparative test) **Tolerance**
AMM - Marketing Authorization			
IV	Utility	Patients (hundreds, thousands) broad recruitment	Measuring effectiveness, benefit, and risk under the usual conditions of prescription **(Pharmacovigilance)**

After obtaining marketing authorization, the drug is prescribed by doctors and veterinarians and dispensed by pharmacists under its first trade name with its DCI.

ÿ **SPC** (Summary of Product Characteristics)

For medicines with a marketing authorization, the laboratory must publish a Summary of Product Characteristics (SmPC) (different from the patient information leaflet) which allows healthcare professionals to know all the product characteristics (composition, indications, instructions for use).

The RCPs are available on the following databases : **Vidal, DMV.**

II.3.2. LABELLING OF VETERINARY MEDICINES

a) Common provisions

The container, outer packaging and possibly the leaflet(s) of the medicine(s) must to be carried, unless an exemption is granted when the marketing authorization is issued:

1) The name of the drug: the common or scientific name alone or preceded by the special name

2) the pharmaceutical form

3) the qualitative and quantitative composition

4) the number of therapeutic units or, failing that, the container capacity

5) the animal species for which this medicinal product is intended, the method administration and route of administration, contraindications, rates and products of dilution for premixes

6) the waiting time, even if equal to zero

7) the expiry date in plain text

8) the name and address of the person responsible for placing the product on the market and, where this person does not does not manufacture the drug; the name and address of the manufacturer

9) the number and date of the MA

10) the manufacturing batch number

11) any special storage precautions, if applicable

12) Depending on the case, the statement: "VETERINARY USE" or " VETERINARY USE A "DISPENSE ONLY ON PRESCRIPTION" or " FOR VETERINARY USE ONLY. DISPENSE ONLY. ON PRESCRIPTION, TO BE KEPT FOR THE REQUIRED PERIOD WAITING FOR MEDICATION"

Furthermore, the presence of an information notice for the user is mandatory. except in cases where all the information that must be included is directly on the packaging.

It must include additional details such as the pharmacotherapeutic class, therapeutic indications, and information the patient needs to know before taking the medication (dosage, contraindications, precautions).
(dose usage, drug interactions, side effects).

b) Supplementary provisions: poisonous substances

All pre-prepared medications containing poisonous substances (substances containing active ingredients that are dangerous to the body) must **in addition,** bear the message "RESPECT THE PRESCRIBED DOSES" in black letters on a red background.

Furthermore, the outer packaging must be designed with care, under the name of the medicine, a white space, intended to receive the regulatory information that it is planned to include it at the time of its release to the public;
This white space is framed by a colored border:

- Red for drugs on list I: Toxic drugs " **schedule** A"
  e.g., (Strychnine) and the Snarcotics " **schedule B"** (ex: Morphine).
- Green for List II: Medicines D " **Table C"** e.g., (Insulin) dangerous

Notes: 1-Tablet drugs: is an old term given to any drug which can only be dispensed with a prescription (There are 3 in the International Pharmacopoeia tables: A, B, C).

2-If a product contains several poisonous substances listed in different categories,
Only the frame corresponding to the most dangerous one will be shown.

II.3.3. ORDER

a) Definition

The order (Ordo = Arrangement = Order) is a document that must be perfectly organized. It allows the prescription user to know and follow their treatment and then the pharmacist to dispense it.
The only people authorized to write a prescription are: doctors, dentists, veterinarians, midwives, laboratory directors biological analyses.

Advice

A prescription must be properly presented, explicit, and perfectly legible.

The pharmacist has the right to refuse a prescription that he deems non-compliant.

b) Diagram of a medical prescription : the prescription must include:

ÿ Identity and qualifications of the prescriber (doctor or veterinarian: name, address, registration number) phone).

ÿ date.

ÿ Identity of the beneficiary animal: species, sex, breed, age, distinguishing marks.

ÿ Identification of the animal's owner (name, surname, address, phone number) phone)

ÿ Drug(s): Name (ND or INN), concentration and total quantity of the active ingredient (by weight, volume or number of packaged units), form, method of administration, dosage, that is to say the prescribed daily quantity, the time of intake and the duration of treatment

ÿ the signature affixed immediately below the last line, so as not to leave no residual space.

CHAPTER III

PHARMACOKINETICS

GOALS

- Describe the different phases of the drug's fate in the body.
- Define the main mechanisms of transmembrane passage of drugs.
- Explain the factors influencing the transmembrane passage of drugs
- To be able to determine, based on the physicochemical characteristics of an active ingredient to explain its ability to cross plasma membranes.

III.1. INTRODUCTION

For a drug to exert its therapeutic effect, it is essential that the active ingredient reaches its site of action. The fate of the drug in The organism is therefore as important as its pharmacological action.

Pharmacokinetics is the **quantitative and qualitative study of the fate** of an active substance contained in a drug after its administration (introduction (by one of the routes of administration) in the body **depending on the time.**
It is one of the pillars of pharmacology.

The goal of pharmacokinetics is to optimize treatment regimens. This allows us to define the pharmaceutical form, frequency, and route of administration. will allow the living, diseased organism to reach blood concentrations of Effective active ingredients while minimizing the occurrence of side effects. In medicine From a veterinary perspective, its main advantage is the ability to adapt **dosages** to different species for future use.

It covers several stages, from absorption, distribution, and metabolism to The elimination of drugs in various organisms. (Table I)

These steps may or may not all be carried out, may or may not follow each other in this order, may or may not be carried out separately or at the same time.

Table IV: Pharmacokinetic parameters (Bousquet-Mélou, 2014)

STEPS	SETTINGS
1. ABSORPTION	Bioavailability
2 DISTRIBUTION	Distribution volume % of plasma protein binding
3. METABOLISM	3.4 Clearance
4. EXCRETION/ELIMINATION	Half-life

For at least one of these phases to occur, the active ingredient (AI) molecule is confronted each time with what are called "biological barriers". These are represented by the cytoplasmic membranes of all tissues in the body (tub digestive, vascular wall, liver, kidney) which separate aqueous spaces called "compartments".

The main compartments are: plasma, interstitial fluid, intracellular fluid cytoplasmic, cerebrospinal fluid

III.2. PASSAGE THROUGH CELL MEMBRANES

III.2.1. CELL MEMBRANE (REVIEW)

The cell membrane is a bilayer of phosphoglycerolipids:

- The interior is made up of the tails of the phosphoglycerolipids; this is the part hydrophobic
- The exterior consists of the phosphoglycerolipid heads, external proteins, and side chains; this is the hydrophilic part

The plasma membrane is a fluid mosaic of phospholipids (60%) and proteins (40%). It exhibits selective permeability:

Hydrophobic or nonpolar (lipophilic) molecules can easily pass through the membrane

ÿ Hydrophilic or polar (lipophobic) molecules require a system of transport ensured by membrane proteins

The ability to cross the phospholipid bilayer is essential for the absorption of the active pharmaceutical ingredient (API) molecule and its distribution in different tissues and spaces. intracellular.

III.2.2. TRANSMEMBRANE TRANSPORT MECHANISMS

Given this structure, the transfer across biological membranes

This can be done through two main processes:

- Passive transport Active transport

III.2.2.1. PASSIVE TRANSPORT

Passive transport is represented by

- Simple or passive diffusion
- Filtration
- Facilitated dissemination
- Pinocytosis

SIMPLE OR PASSIVE DIFFUSION

This is the most important mode of transfer, estimated to account for 90% of the transfer of medication. It is determined by 4 parameters:

- The concentration gradient.
- Lipophilicity and molecule size.
- The non-ionized fraction of the molecule and its pKa.
- The pH of the environment.

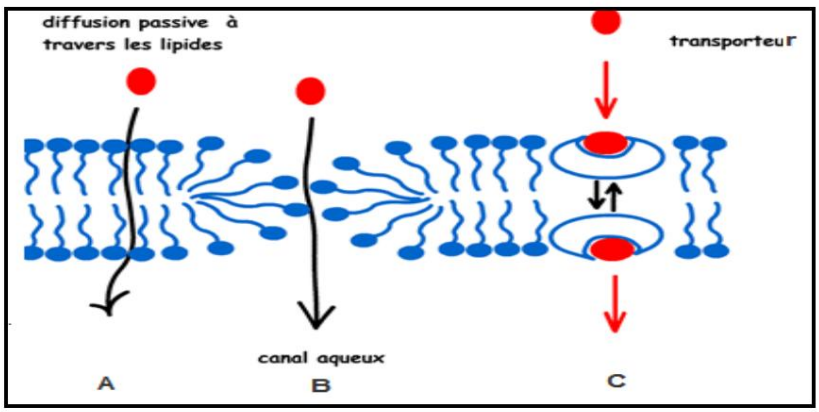


Figure 3: Passive diffusion (through lipids, B: filtration, C: facilitated diffusion) (Bensegueni Tounsi, 2013)

A) Concentration gradient

The penetration of molecules through the lipoprotein film occurs by simple dissolution; transmembrane passage occurs primarily as a result of differences concentration gradient between the two faces of the membrane;

Dissolved molecules move from the area of higher concentration to the area of lower concentration, until the concentrations on either side of the membrane

They balance each other out. This transition requires no energy.

B) Lipophilia

Lipophilic and **hydrophilic** (or hydrophobic and lipophobic) character is defined by The solubility of molecules in media of low polarity or, conversely, high polarity. Blood plasma, interstitial fluid, and cytoplasm constitute aqueous media of high polarity (favoring the ionization of molecules), while lipids, at
less so within a membrane layer and fat are nonpolar media.
Therefore, lipophilicity is expressed by the degree of liposolubility of the molecule, that is to say its ability to blend into the lipid fraction of the membrane.

*** **Water-soluble molecules** (highly ionizable, polar) e.g., Na^+ , K^+, Cl^-glucose, proteins penetrate very little, which explains, for example, the poor absorption of strong acids, such as Streptomycin, administered orally

*** The substances that penetrate membranes most rapidly are **fat-soluble** substances of **small size,** for example: fat-soluble vitamins, hormones, O_2, CO_2 , N_2)

C) Ionization

Water is a polar solvent, and the molecules dissolved in water are ionized and Therefore, **they are unable** to cross the cell membrane. Only the non-ionized form of a drug, if it is sufficiently lipid-soluble, is capable of crossing the membrane. cellular.

The state of ionization depends on the pKa (which expresses the dissociation constant of the molecule) and the pH of the medium. The pKa is defined as the pH at which an acid exists in a 50% ionized form and 50% non-ionized form.

The ratio of ionized form to non-ionized form is defined by the Henderson-Hammer equation. Hasselbalch.

For a weak base (B): pH=pKa+log [HB+]/[B]

For a weak acid (A): pH=pKa+log [A-]/[HA]

Therefore, depending on the pH of the environment in which the drug is found, its ratio (ionized fraction/non-ionized fraction) varies, and thus its absorption is variable. (In
In adult men, the plasma pH is 7.4, in the stomach: 2, in the
jejunum: (8).

~ For **a weak acid:**

- At alkaline pH, **ionization is significant ,** resulting in a larger ionized fraction, which will limit the transmembrane passage of this substance.
- At acidic pH , **ionization is low,** the non-ionized fraction is larger, the
The drug will cross cell membranes more effectively.

~ For **a weak base,** the opposite will be observed:

- At alkaline pH, **ionization is low, so** the drug will easily cross the membranes.
cellular
- At acidic pH, **ionization will be greater,** resulting in a larger ionized fraction, and the drug will have difficulty passing through cell membranes.

*** Simple diffusion allows the passage of **lipid-soluble, nonpolar ,** and **non-ionized molecules;** it occurs **along a concentration gradient, without energy, without specific transporter** and it is a **non-saturable** phenomenon

FILTRATION

This transport process simply occurs through the membrane pores.

It concerns **water-soluble** molecules of **small size** and **low molecular weight:** water, urea, ions (K+ , Cl-).

It is in the blood capillaries that the pores are most numerous and have the largest diameter, particularly in the kidneys: filtration
The glomerular system is an essential route for eliminating drugs and toxins.

III.2.2.2. EASY DISTRIBUTION

Facilitated broadcasting differs from simple broadcasting by a higher speed.
not proportional to the concentration gradient.

The movement of the drug by facilitated diffusion across the membrane
they move in the direction of the gradient, without energy, and are facilitated by a specific transporter (membrane transport protein) subject to saturation or depletion phenomena competition (possible drug interactions).

III.2.2.3. PINOCYTOSIS

Pinocytosis is an important transport process in cells of
mammals, particularly in intestinal epithelial cells and cells
renal tubules.

It corresponds to an invagination of the cell membrane to encompass, for example, a **lipid droplet** whose contents are then integrated into the cytoplasm; it is
quite analogous to phagocytosis which occurs with solid elements.

III.2.2.4. ACTIVE TRANSPORT

Numerous natural molecules (amino acids, Mg+2 ions, Ca+2 ions, sugars)
They cross membranes thanks to the intervention of a **specific transport molecule.** This process **requires energy against a concentration gradient,** meaning that the concentration of the compound can be higher than
the other side of the membrane in question. This is a saturable phenomenon; it can be inhibited. or subject to competition between transported molecules (possible drug interactions).

The formation of this complex occurs on one side of the membrane and its
dissociation onto the other, thus releasing the transported molecule.

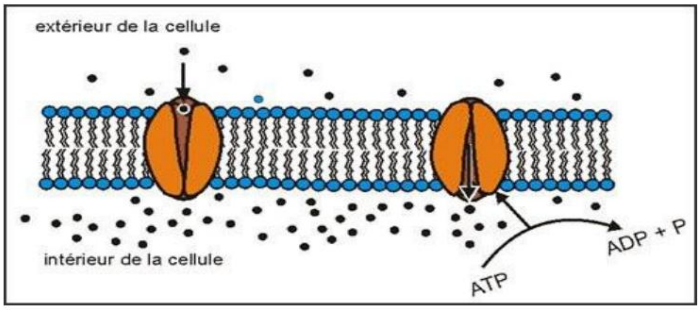


Figure 4: Active transport (Loichot and Gima, 2005)

SPECIAL CASE OF WATER

It is a very polar molecule, but very small in size which in some
While very fluid membranes allow water to pass through slowly, in most cases, the water molecule requires a transport protein. For example, water porins are protein channels that facilitate the passage of water molecules.

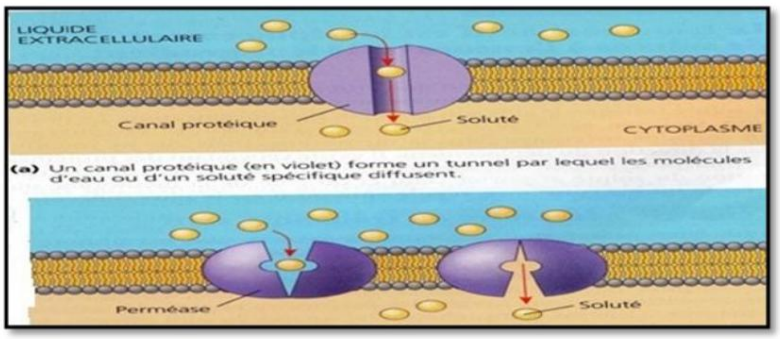


Figure 5: Receptor transport protein (Jaspard E., 2012)

Transport proteins are generally very selective. For example, the passage of glucose into red blood cells: this mechanism uses very specific proteins that do not allow any other glucose isomer to pass through.

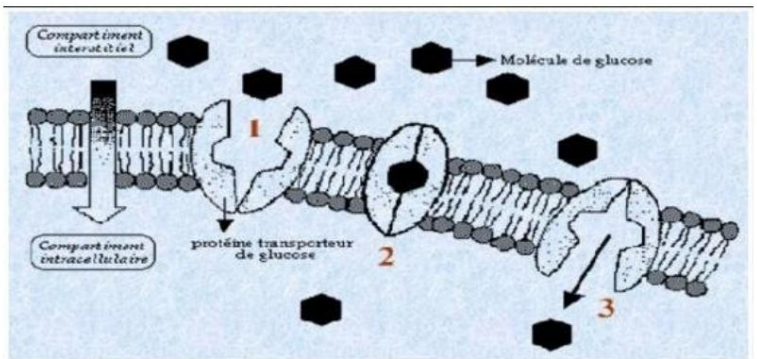


Figure 6: Glucose-specific transporter protein (Selouani, 2014)

RECEPTOR PROTEINS

A membrane protein can carry a binding site whose shape matches that of a chemical messenger, such as a hormone.

The messenger (stimulus) can cause a change in the conformation of the protein (receptor), following this, the cytoplasmic part of the protein triggers a cascade of chemical reactions in the cell and allows the passage of the molecule.

Example: the role of insulin in the passage of glucose into cells of the organism (Except in the case of the nerve cell and the red blood cell).

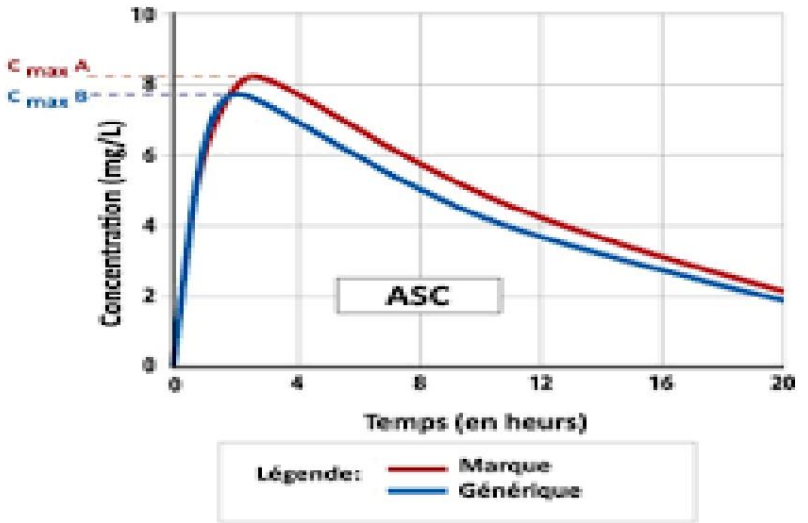
III.3. BIOAVAILABILITY, BIOEQUIVALENCE

Only a fraction of the administered amount is absorbed and reaches the sites of biological or toxic action.

• **The bioavailability** of a xenobiotic corresponds to the **amount** of active ingredient released from the pharmaceutical form or (the **fraction of the** administered dose) which reaches in general traffic **and the speed** at which it gets there.

• **Bioequivalence** applies to an active ingredient in a given pharmaceutical form and is only valid for a specific route of administration.

Quantity is assessed by AUC. Velocity is assessed by: Tmax and Cmax.



C_{max} concentration maximale;
(ASC) surface totale de l'aire sous la courbe de la concentration

Figure 7: Plasma concentration curves of two bioequivalent drugs (ACMTS, 2011)

Two pharmaceutical products will be considered **bioequivalent** if they provide in the body similar **curves showing the evolution** of concentrations over time.

Two active ingredients are said to be **bioequivalent** when, administered at the same dose, they produce the same amount of liquid in the same way as other active ingredients. at concentration, they normally produce **the same effects.**

III.3.1. BIOAVAILABILITY ASSESSMENT

The bioavailability of a drug is defined as the ratio between the amount of active ingredient active ingredient reaching the general bloodstream and the amount administered.
It is associated with the speed at which it reaches the target and the maximum concentration obtained. is therefore expressed by three parameters.
Bioavailability describes how an active ingredient becomes available to produce its Biological action. It is denoted by the letter F (ratio of quantities); it is expressed by a percentage (F%). It can take any value between 1 (zero bioavailability) and 100 (total bioavailability).
By definition, a drug administered intravenously will have a bioavailability absolute of 1 (F=1), i.e. 100% (total absorption).

Note : The curve after **IV** administration describes the **disappearance of the drug** from the plasma compartment. This is due to the distribution of the drug into other compartments and its elimination.
After oral administration , the curve is **biphasic :** it first describes the increase in plasma concentrations linked to drug absorption and then the decrease in these concentrations linked to its distribution and elimination. The point where the **The concentration is at its maximum,** corresponding to an **equilibrium** between the amount of drug which is **absorbed** and that which **disappears** from the plasma.

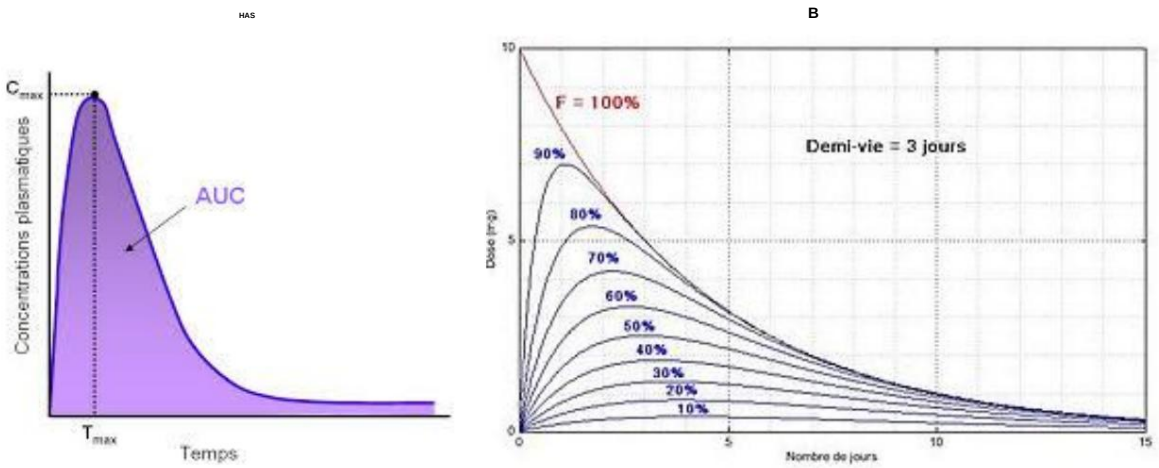


Figure 8: A; Area under the curve (ANSM, 2016), and B; Evaluation of absolute bioavailability

Why is it important to know about bioavailability?

The administered dose (external dose) is not necessarily equal to the dose that will actually have an effect, also called the internal dose. The therapist wants to know the patient's actual exposure, which is related to the internal dose; the relationship between the administered dose and The internal dose is determined by the bioavailability factor. The measurement of the Bioavailability is also informative for topically administered drugs, allowing for the anticipation of systemic effects or drug residues in veterinary medicine. There are two types of bioavailability: absolute and relative.

III.3.1.1. ABSOLUTE BIOAVAILABILITY

Absolute bioavailability allows us to define the ratio of the quantity of principle active ingredient absorbed by any route compared to the intravenous route (F%=100%: total abs) = the ratio of the area under the "AUC" curve of the given route and that of the IV (same dose). Its estimation involves comparing exposure after extravascular administration with that obtained with a intravenous route which serves as the reference (because it is presumed to be 100%, which is generally the case).

EX: Absolute bioavailability via oral route:

F = Oral AUC ÿ for the same dose administered via both routes **IV AUC**

If identical doses for both routes were not possible :

F = oral AUC x IV dose

AUC IV oral dose

III.3.1.2. RELATIVE BIOAVAILABILITY

Relative bioavailability involves comparing several pharmaceutical presentations of the same drug; it is the ratio of the area under the AUC curve to the concentrations plasma of a given form and of the usual form used – without reference to track IV.

The purpose of relative bioavailability is to compare, relatively, bioavailabilities in order, for example, to choose the best method of administration (to fasting or in food for example).

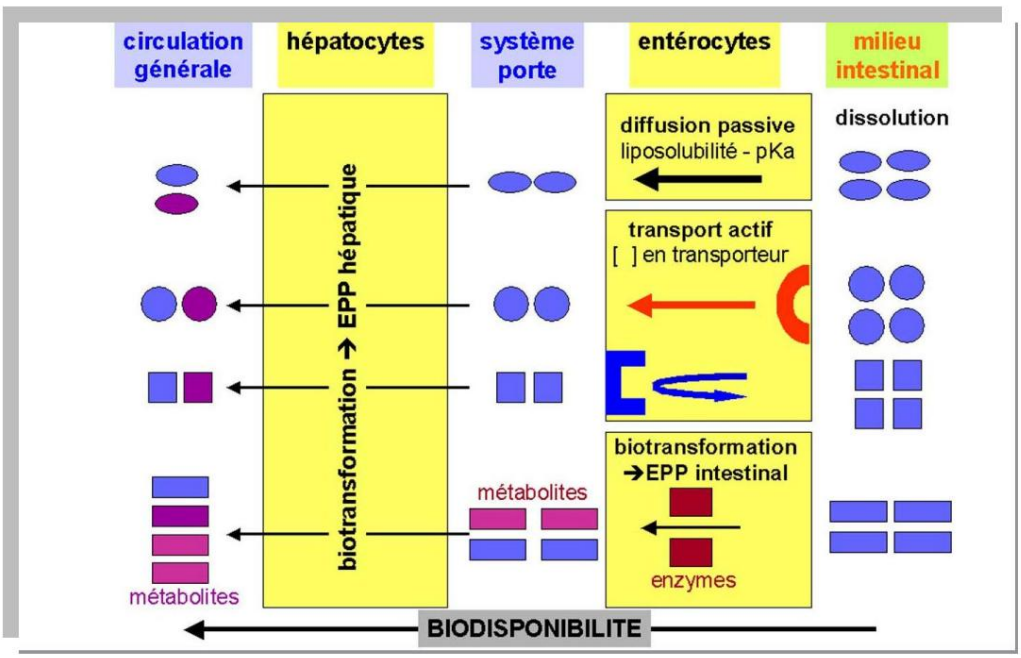


Figure 9: Schematic representation of oral bioavailability (Vincent, 2019)

III.4. ABSORBATION (PK1)

GOALS :

- Understand absorption and distribution and explain the factors influencing it
- Define and measure a distribution volume and its significance
- Distinguish the factors that allow for the assessment of the risk of drug interactions involving plasma protein binding
- Understanding the different metabolic pathways
- Understand the consequences of drug metabolism
- Consider the potential benefits of a prodrug • Interpret information on drug metabolism
- Describe the phenomena of enzyme induction and inhibition and their pharmacokinetic and clinical consequences to avoid interactions drug-related issues involving these phenomena.

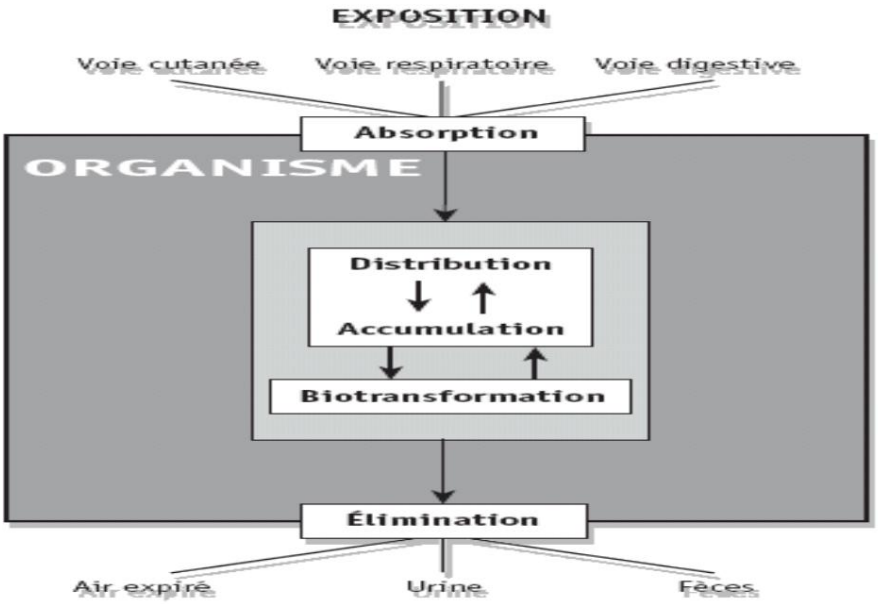


Figure 10: Pharmacokinetic steps (Viau and Tardif., 2003)

III.4.1. DEFINITIONS

It concerns the first passage of the active ingredient (AI) molecule from its administrative point up to general traffic.

Absorption determines the bioavailability of the active ingredient, that is, the fraction of the dose administered which will be available to act at the level of an active site.

Depending on the method of administration, we distinguish:

• **Mediate absorption:** the drug is administered outside the body
or in a light, it must pass through one or more membranes (e.g., cutaneous application)
or mucous membrane, oral administration)

• **Immediate absorption:** the medication is introduced by force, directly
in the extravascular space within a tissue (e.g., administration by injection)
parenteral (SC, IM, IP)

**** During **IV** administration , which leads to the direct introduction of the drug into the blood, **the absorption phase is eliminated**

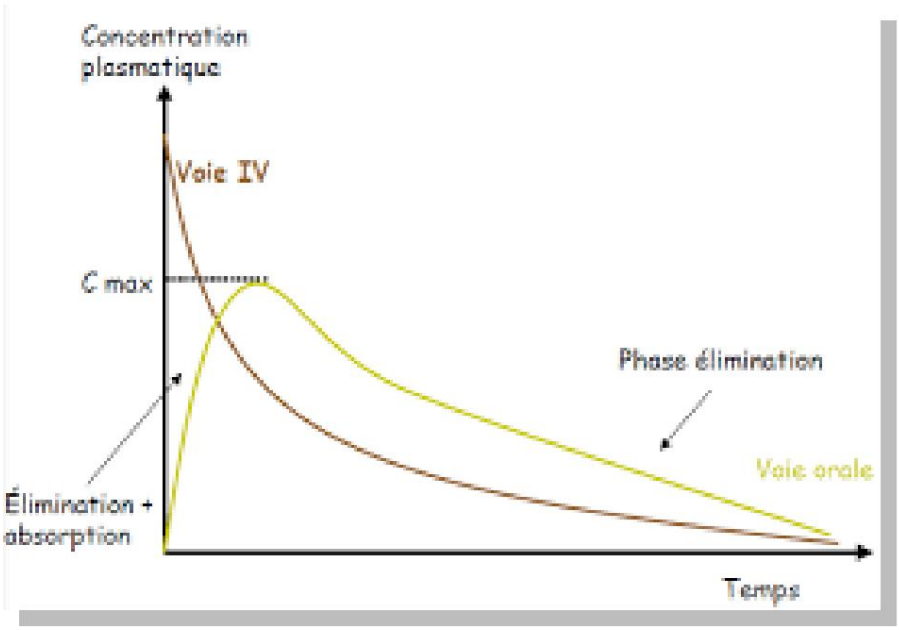


Figure 11: Pharmacokinetic profile of a drug administered intravenously and orally (Lùllmann et al, 2010)

III.4.2. LOCAL (TOPICAL) ABSORPTION

III.4.2.1. PERCUTANEOUS

Medications can be absorbed through the skin after topical application; however, the stratum corneum presents an effective barrier to the mobility of the most medications.

In most cases, intact skin allows the passage of small substances
lipophilic, but effectively delays the diffusion of water-soluble molecules.

Generally, lipid-insoluble drugs penetrate the skin slowly compared to their absorption rate through other substances.
body membranes.

Damaged, inflamed, or hyperthermic skin allows penetration of
many medications can cross the skin barrier.

III.4.2.2.MUCOSA

It is easier than through the skin, due to the absence of the stratum corneum and the dense vascularization. It is triggered either at the level of the ocular mucosa,
Rhinopharyngeal or vaginal. Extramammary diffusion is very limited.

Note: Some medications are administered for local distribution, for example:
ocular (conjunctival sac), nasal (nasal mucosa), auricular.
It is important to know that it is often difficult to limit the passage of these medications into the bloodstream.
In general, side effects may occur. For example, nasal vasoconstrictors.
are likely to cause peripheral vasoconstriction with hypertension

III.4.3. ABSORPTION VIA RESPIRATORY ROUTE

In principle, it is easier than through the skin due to the dense blood supply, the large contact area (100 m2 in humans) and its very thin epithelium.
Respiratory function allows for intense absorption of fat-soluble chemicals.

The absorption of medications via the lungs is especially taken advantage of by
anesthesia with gaseous or volatile anesthetics.

III.4.4. ABSORPTION VIA THE DIGESTIVE ROUTE

This is a process by which the drug enters the general circulation
from the digestive tract.

The drug is administered either orally, with absorption possible via
via the oral, gastric or intestinal mucosa, or via the rectal route.

III.4.4.1. DETERMINING FACTORS

Several factors affect gastrointestinal absorption. These include those related to the drug (physicochemical characteristics) and those dependent on the patient (entity). biological). (Figure below)

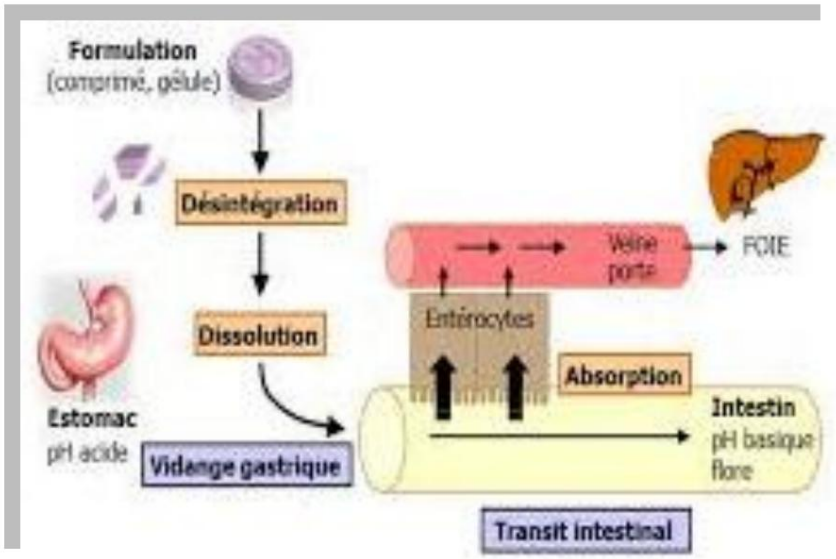


Figure 12: Factors in the absorption of a solid drug (Laffont, 2011)

Pharmaceutical form and rate of dissolution

The pharmaceutical form plays an important role in the different phases which lead to the dissolution of the drug, an essential condition for its absorption.
The liquid form (syrup, solution) crosses the digestive barrier more quickly than other solid forms (tablet, capsule).

In descending order, the flow rate is: aqueous solutions > solutions oily > suspensions > solids

Drug formulations that dissolve quickly (syrup, solution, ampoule) have a shorter onset of action than formulations designed to have a slow and continuous dissolution (oily solution).

There are specific galenic forms whose dissolution follows certain patterns. specific kinetics:

- Extended-release (ER) formulation: releases a constant amount of drug per unit of time. This helps maintain plasma concentrations within the therapeutic range for a longer period.

- Delayed release form: example of an active ingredient released and absorbed in the intestine but not in the stomach e.g. gastro-resistant coated tablets.

The pharmaceutical phase depends **on disintegration,** the galenic form, and **solubility.** of the active ingredient and **the size** of the molecule.

MOLECULE SIZE

Small molecules are absorbed more easily than large molecules. Small, water-soluble molecules (water, alcohol) are well absorbed at the level of the stomach lining.

MOLECULE SOLUBILITY

The digestive mucosa can be considered a porous lipoprotein membrane. Absorption therefore follows the rules of transmembrane passage. It occurs primarily through passive diffusion. This means that these are the substances fat-soluble which will be well absorbed by the digestive mucosa, but a slightly water-soluble character is necessary.

Thus, some **exclusively lipid-soluble** medications **(petroleum jelly** and **paraffin)** do not pass through the digestive tract. These two medications are used as laxatives.

Similarly, **sulfaguanidine, which is very highly ionized** throughout the tube digestive is used for the local treatment of intestinal infections.

pH OF THE DIGESTIVE TRACT

- **The stomach:** weak acids (salicylates, sulfonamides, phenols) are very poorly ionized at the acidic pH of the stomach. Their absorption is therefore rapid and intense through the gastric mucosa. Conversely, weak bases (alkaloids, morphine, ephedrine, strychnine) are in ionized form and are not absorbed.
- **The intestine** (alkaline pH): weak acids are less well absorbed than in the stomach. As for weak bases, their absorption is excellent at this level, since the The non-ionized, fat-soluble form predominates.

GASTRIC EMPTYING

Any factor that can slow down or increase gastric emptying alters the rate of drug absorption.
(Example: **Metoclopramide** (PRIMPERAN)=
Antiemetic: accelerates gastric emptying of weak bases which will quickly gain weight
the intestine where their absorption is maximal).

Gastric motility determines the rate of absorption, which will be more or less
slowed down by the quantity and nature of the food, e.g., in polygastric animals, cellulose
binds to many drug molecules and delays the therapeutic response which
will be very low or zero.

In general, it can be understood that taking a drug through an IV stomach promotes absorption.

DIGESTIVE METABOLISM

Enzymes from the gastrointestinal mucosa (e.g., cytochrome P450, esterase) as well as
those of the bacterial flora in the lumen of the digestive tract can lead to
the degradation or metabolic transformation of certain drugs.
For example, peptides that cannot be administered orally due to their degradation by microorganisms
in the gastrointestinal tract.

For some medications, the transformation at the level of the mucous membrane of the tube
The digestive process leads to the release of an active ingredient:

The administered drug is not active (this is called a prodrug or
prodrug) but, its lipid-soluble structure allows passage through the membranes of
the gastrointestinal mucosa, where it will be partially metabolized to release an active compound
(less fat-soluble).

AREA OF THE ABSORBENT SURFACE

The surface area available for absorption is a major determinant of the rate
absorption.

The larger the surface area, the faster the absorption. For this reason, the
Oral medications are designed to be absorbed by the small intestine, which offers more
large absorption surface;

(200 to 300 m2 compared to 1 m2 at the level of the stomach in humans) thanks to the villi and microvilli, also due to vascularization and peristaltic movements.

FIRST PASS HEPATIC EFFECT

Once absorbed by the gastrointestinal mucosa, the drug enters the portal circulation, carrying it to the liver where it can be metabolized (more or less).
less completely) before arriving in general traffic. This is a process called " first-pass hepatic effect ».

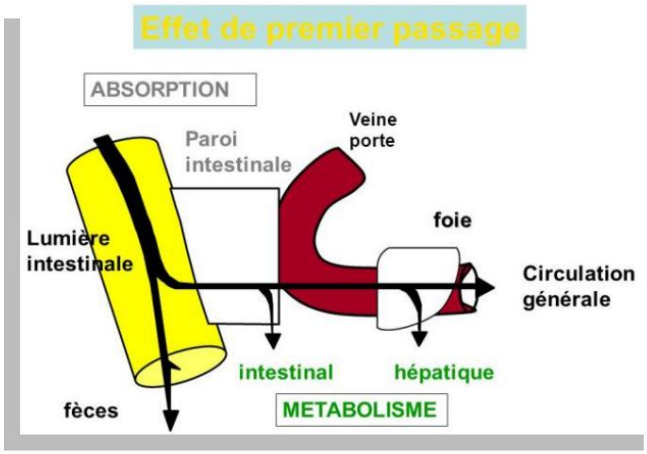


Figure 13: Schematic representation of the first hepatic passage (Bousquet-Mélou A, 2019b)

Note : Other organs are also capable of metabolizing drugs during the first passage (lungs, stomach and intestines) but the liver is quantitatively the most important.

The first-pass hepatic effect can lead to significant drug loss and thus a reduction in therapeutic effect. The therapeutic dosages used take this into account.

III.4.5. PARENTERAL ABSORPTION

III.4.5.1. INTRAVENOUS ROUTE (IV)

The administered drug passes directly into the general circulation, so the effects obtained are very rapid.

Too rapid an injection can lead to serious cardiorespiratory problems (hypotension, respiratory cardiac arrhythmia) related to concentration effects
plasma.

III.4.5.2. SUBCUTANEOUS (SC) AND INTRAMUSCULAR (IM) ROUTE

The IM and SC routes, like the IV route, allow for rapid absorption if there is a vascular bed with high local blood flow at the injection site. The absorption rate of drugs via these two routes is generally similar; the IM route is
slightly faster due to better vascularization. Blood reabsorption of
The medication is absorbed by passive diffusion or filtration through the pores.

III.4.5.3.INTRAPERITONEAL ROUTE

Substances administered intraperitoneally are rapidly absorbed,
The peritoneum constitutes a large, permeable surface area that is well-irrigated by capillaries. blood and lymphatic vessels.

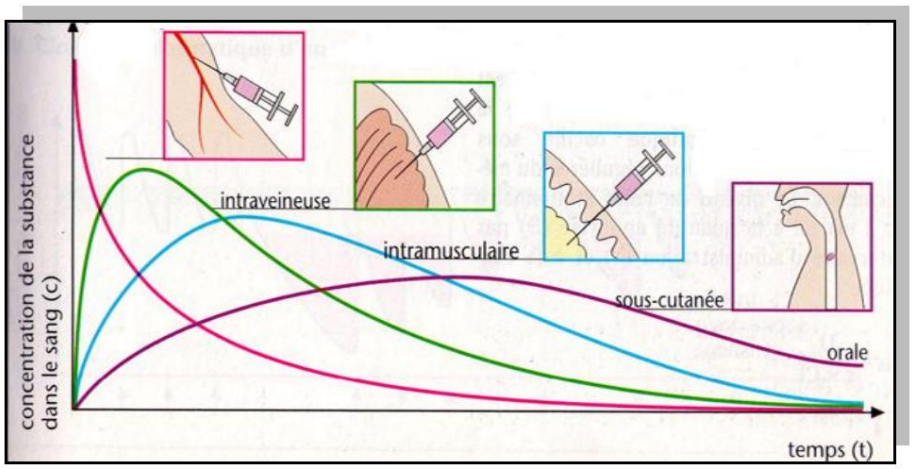


Figure 14: Mode of action and plasma kinetics (Joachim, 2015)

III.4.6. ABSORPTION EVALUATION

The amount of the drug that reaches the general (or systemic) circulation depends on the route of administration, the dose administered, and the amount absorbed, but
also, other pre-systemic elimination processes:

- Degradation in the intestinal lumen
- Biotransformation at the level of intestinal epithelial cells
- Significant hepatic uptake on the first pass

III.5. DISTRIBUTION (PK2)

GOALS

- Define the distribution and explain the factors influencing it
- Define and measure a distribution volume
- To understand the factors that allow for the assessment of the risk of drug interactions involving the binding of drugs to plasma proteins
- Understanding the meaning of a distribution volume

III.5.1. DEFINITIONS

After absorption, drug molecules are distributed to various tissues via the general circulation; blood flow is therefore an important factor.

to be considered when assessing the amount of active pharmaceutical ingredients (APIs) that this organ receives per unit of time. We generally arrive at a balance between a **bound,** non-diffused form, and therefore **without action** and in a **free form,** capable of diffusing into the tissues and therefore **active.**

Interaction with plasma proteins ensures **temporary functions fixation** (storage and transport) **and protects the molecule from degradation.**

BLOOD TRANSPORT

In the blood, the drug exists in two forms: a free form and a
In its bound form, this binding occurs primarily through attachment to plasma proteins and secondarily to the formed elements of the blood (erythrocytes, polymorphonuclear leukocytes, platelets).

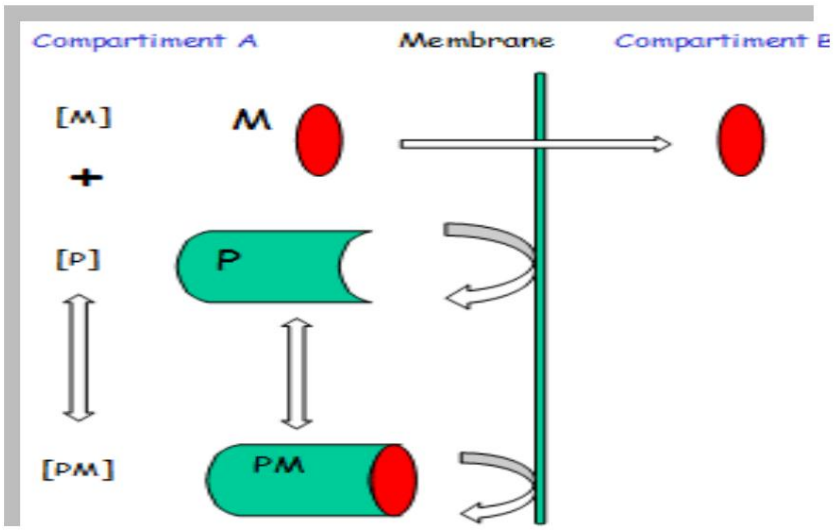
ATTACHMENT TO PLASMA PROTEINS

The binding **(storage and transport)** of chemical substances to plasma proteins is generally **reversible;** otherwise, the xenobiotic becomes a poison.
The binding proteins are primarily **serum albumins** and secondarily **lipoproteins (globulins).**

- Albumins primarily bind acidic molecules: salicylates, sulfonamides, barbiturates.

Globulins bind highly lipophilic substances: vitamins, hormones, and certain metals. Some medications, similar to biological compounds (sex steroids, corticosteroids), bind to specific transport globulins.

corresponding natural numbers.



(M: drug, P: plasma protein)

Figure 15: Transmembrane passage of the drug bound to the plasma protein (Jonville Bera, 2011)

***** This is the determination of the proportions "in Vitro" and "in Vivo" of the forms free and linked which will determine the dosage and number of doses per day.**

Drug binding to proteins is conditioned by the properties physicochemical properties of the molecule which can be strongly or weakly bound to proteins plasma:

- The free form is diffusible across the membrane, therefore it is the only active form and the only one Eliminable. This gives them a quick but short-lived effect.
- The bound form remains in the blood, due to its weight and molecular size (drug + protein) have become too large to allow passage through the cell wall endothelial. This bound form constitutes a reserve that can be mobilized as the disappearance of the free form. This form of reserve is temporary and it allows for maintain a blood/tissue concentration gradient. Highly bound drugs will a slower but prolonged action: they constitute natural delayed forms.

Understanding the physicochemical nature of molecules helps avoid drug interactions that could lead to side effects.
serious.

III.5.2. CONCEPT OF DRUG INTERACTION

This occurs when two molecules compete for the same protein.
Plasma concentration is conditioned and explained by the specific affinity of each molecule.

Example 1: Simultaneous administration of acetylsalicylic acid and a hypoglycemic agent Oral administration can lead to severe hypoglycemia in diabetics. Knowing the nature acetylsalicylic acid has a tropism for albumins and hypoglycemic molecules also bind to plasma proteins.
Example 2: Many lipophilic drugs are contraindicated in the
pregnant females, because they interfere with the hormones circulating in the blood and due to the high permeability of the placenta to the general circulation.
Example 3: 99% of drug A is bound to plasma proteins, activity
Therapeutic effect is achieved with 1% of the product free and little distributed outside the plasma.

If drug B displaces A by 1%, reducing protein binding to 98%, the
double the free fraction. Although some of this free fraction diffuses out of the plasma, the consequences of such an increase in the free fraction can be serious when
the therapeutic index of a drug is narrow

However, a 1% shift in A is not significant when the percentage of plasma protein binding is low because changes in the free fraction are then insignificant; otherwise, the therapeutic index is wide.

III.5.3. TISSUE DIFFUSION

To be absorbed, medications must pass through tissue membranes.
The mechanisms of transmembrane drug passage are identical to those
exposed for absorption.

This distribution depends on lipophilicity, ionization, and molecule size, but also on tissue perfusion rate and tissue affinity. Therefore, the distribution is divided into three main compartments:

èr 1 **Compartment:** "the most vascularized tissues": contains all the vital organs (lungs, liver, kidneys, brain, heart)

2nd **Compartment:** "moderately irrigated tissues": includes the muscles skeletal structures, skin, bone marrow, smooth muscles, certain glands

3rd **Compartment:** "the least irrigated tissues": includes adipose tissue, the cartilage, bone tissue, tendons

III.5.4. MODIFYING FACTORS

In addition to the physicochemical properties of the drug molecule (lipophilic, degree of ionization), blood and tissue flow, other factors can modify absorption:

III.5.4.1. PROTEIN BOND

ÿ Competition between molecules for plasma proteins (interaction (medicinal).

ÿ The decrease in plasma protein levels during acute infections (decrease albumin and increased gamma globulins (immune defenses), nephrosis (leakage of plasma proteins through the kidney), or even significant burns (direct loss of plasma due to increased capillary permeability).

III.5.4.2. MOLECULAR AFFINITY

This is explained by the inherent tropism of certain molecules towards certain fabrics:

ÿ Adipose tissue is considered a reservoir of fat-soluble substances, such as The fixation of carotenoids in animal fats accentuates this phenomenon. Because blood flow is low, elimination is therefore very slow. The known metabolism of excess fluoride fixation in dental tissue, these Since fluoro-calcium phosphobonds are irreversible, they cause browning. dental.

III.5.4.3. BIOLOGICAL BARRIERS

During distribution and elimination, a drug may or may not pass through.
certain "physiological" barriers (blood-brain, placental and mammary).

CENTRAL NERVOUS SYSTEM (CNS)

To reach the extracellular fluid of the CNS, the molecules present in the
capillaries must cross the **blood-brain barrier:** also called **hemato-**

The meningeal barrier is a typical lipid barrier, highly selective for foreign molecules (xenobiotics), preventing the passage of ionized and non-lipid-soluble substances. However, nervous tissue remains highly lipophilic due to its structure.

Histologically, this lipophilicity is countered by a barrier made up of cells
endothelial cells are very tightly joined, and in addition the number and size of membrane pores are very reduced, which makes the filtration phenomenon impossible.

Most essential substances, such as amino acids and glucose
would be transported to the brain by selective active transport mechanisms.

Example: **penicillin ,** which is a water-soluble antibiotic molecule ionized at pH
In the plasma, it therefore exhibits physicochemical properties that prevent it from reaching the CNS. However, during meningitis, for example, the permeability of the nerve tissue membrane changes and is exploited in the
treatment and achieving the desired therapeutic effect.

FETO-MATERNAL (PLACENCENTAL BARRIER)

Distribution at this level is very important, as the placenta is highly permeable.
constitutes a non-selective open barrier, hence the numerous contraindications in
pregnant females.

Two main factors need to be considered:

The type of placenta

The affinity and solubility of drug molecules

- **The type of placenta**

In general, the permeability of different types of placenta increases in the following order:

ÿ Epithelio-chorial (horse, pig).
ÿ Syndesmo-chorial (ruminants).
ÿ Endotheliochorial (carnivorous).
ÿ Hemochorial (primates, rodents).

- **Affinity and solubility of drug molecules:** Most of Substances that penetrate the placental membranes by passive diffusion. Nutrients, such as glucose, amino acids, minerals, and even certain vitamins, are actively transported across the placenta.

Redistribution phenomenon: It takes place between two tissues, one with high vascularization and low affinity, the other with low vascularization and high affinity.

When a molecule is highly lipid-soluble and when its administration is via a rapid route. When the molecule is highly lipid-soluble and when administration is by a fast track.

Example: The barbiturate "penthiobarbital" (a general anesthetic administered (via IV route), this molecule is initially distributed to the brain, the principle The active ingredient finds its receptors and produces an anesthetic effect within 30 seconds of IV injection, due to the significant blood flow. However, because of its high lipid solubility, the molecule will cross the blood-brain barrier again in the opposite direction. redistribute and diffuse into less irrigated peripheral tissues such as the tissue In cases of adipose tissue, it is said that: "the medication is out of circulation".

As fats become enriched, plasma concentration decreases; in Depending on this concentration gradient, the barbiturate diffuses out of the brain.

The pharmacological response results in the cessation of the anesthetic effect because there are no receptors in adipose tissue.

This explains the rapid but short-lived anesthetic effect of thiobarbiturates. This problem arises in obese patients in human medicine and in veterinary practice with very obese animals.

MAMMARY GLAND

The epithelium of the mammary gland, like other biological membranes, is a lipid barrier and many drugs rapidly diffuse from the plasma into the Milk. The pH of milk varies somewhat, but in goats and cows it is generally 6.5 to 6.8 in the absence of mastitis. Weak bases tend to accumulate in milk because the ionized, non-diffusible fraction of the drug is more concentrated there. large. The opposite is true for acidic drugs.

III.5.5.CONCEPT OF DISTRIBUTION VOLUME

The distribution volume (Vd) is defined as the fictitious volume (“apparent”, Virtual, theoretical) in which a quantity of medication (M) is distributed to be in equilibrium with plasma concentration (Cm).
Vd is calculated as the ratio of the quantity of drug administered (mg) to the plasma concentration of the drug (mg/l) once equilibrium is reached.

An active pharmaceutical ingredient (API) with a high affinity for tissues will have a large distribution volume; conversely, an API that remains in the blood compartment will have a smaller volume. distribution is low and close to the blood volume.

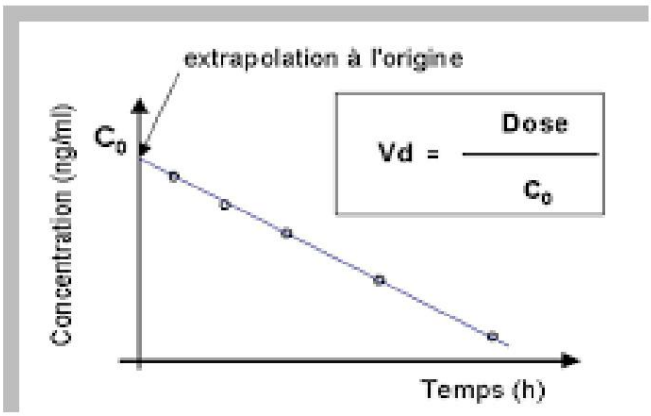


Figure 16: Volume of distribution of an intravenously administered drug (Anonymous, 2023)

In summary,

This distribution allows us to distinguish several types of xenobiotics: neutral and fat-soluble compounds that exhibit a broad and homogeneous distribution. throughout the body

- neutral or ionizable, water-soluble compounds that exhibit a distribution extracellular

- acidic, lipid-soluble compounds with extracellular distribution

- basic fat-soluble compounds that exhibit intracellular distribution

Once it reaches the plasma compartment, the drug distributes itself into different compartments either to reach its receptor and trigger a response tissue, either to be metabolized and then eliminated, or to be fixed in a non-specific or be stored for extended periods in sectors constituting a deep compartment such as adipose tissue.

Finally, this distribution of molecules explains their sites of action. pharmacodynamics, the localization of veterinary drug residues in food of animal origin and their withdrawal period.

III.6. BIOTRANSFORMATION-METABOLIZATION (PK3)

GOALS

- Describe the different metabolic pathways.
- Explain the consequences of drug metabolism.
- Be able to explain the benefits that a pro-drug approach can have.
- Interpret information on drug metabolism.
- Be able to explain the phenomena of enzyme induction and inhibition and their pharmacokinetic and clinical consequences to avoid interactions drug-related issues involving these phenomena.

III.6.1. DEFINITIONS

Biotransformations can be defined as a set of reactions biochemical, generally enzymatic, processes that modify the structure chemical composition of substances introduced into the body.

Many tissues can carry out this biotransformation (liver, digestive tract, kidneys, lungs, skin, plasma, cerebrospinal fluid, synovial fluid).

However, the liver remains the primary site of these biotransformations, which are carried out by the enzymatic machinery of hepatocytes. This is explained by the very high blood flow. The liver, a detoxifying organ, is important compared to other organs: it receives approximately 1.5 liters of blood per minute (1.2 liters via the portal vein and 0.3 liters via the hepatic artery).

*** The main purpose of these hepatic biotransformations is to render the molecule under form of a **highly water-soluble ionized metabolite therefore easily Eliminable.** The liver's detoxification function depends on this.

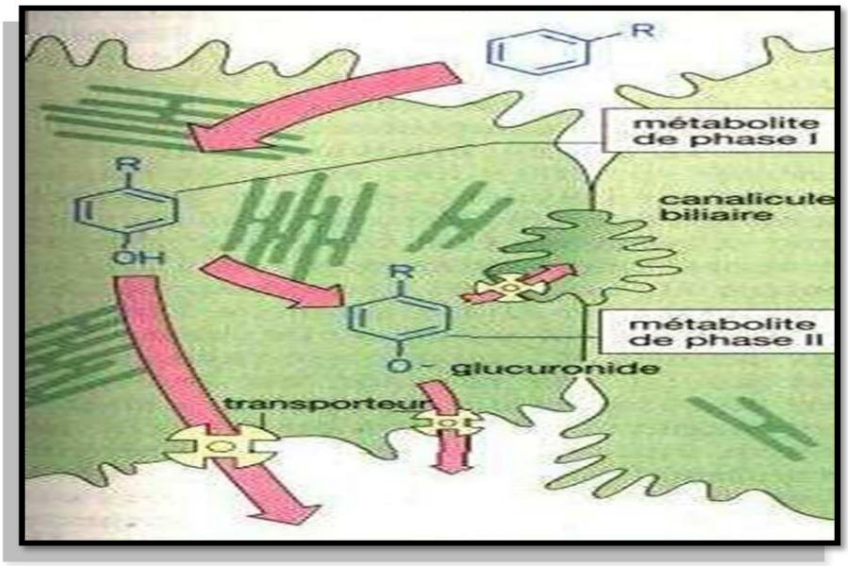


Figure 17: Fate of a molecule in the liver (Lüllmann et al, 1998)

The action of liver enzymes varies greatly depending on the nature (particularities structural and their functional groups) of the substance in question.

There are two types of biotransformations: phase I reactions (reactions of degradations) and the phase II reaction (conjugation reactions).

In short, they can either alter their general structure, split, or merge. the molecules.

Lipid-soluble molecules easily penetrate the hepatocyte and undergo the the most intense degradation and conjugation reactions.

- Conversely, water-soluble molecules pass weakly through biological membranes and are therefore poorly biotransformed.

III.6.2. PHASE I REACTIONS

The enzymes responsible for all these reactions are concentrated mainly in the endoplasmic reticulum and in the mitochondria of
hepatocytes.

Phase I reactions often result in biologically active metabolites.
more active but sometimes more or less toxic.
These degradation reactions are represented by:

- ÿ Oxidation.
- ÿ The reduction.
- ÿ Hydrolysis.

I.6.2.1. OXIDATION REACTIONS

These are very common reactions; they are mostly localized in the
hepatic microsomes.

MICROSOMAL OXIDATION SYSTEM

It is an enzyme complex abundant in the liver, located in the microsomes of hepatocytes. It functions thanks to a specific hemoprotein: cytochrome P450, which owes its name to the fact that in its reduced form, it can bind
a carbon monoxide molecule and form a stable complex whose absorption spectrum is characterized by a maximum at 450 nm.
This cytochrome P450 allows the oxidation of xenobiotics through its coupling to a
electron transfer system (NADPH, FAD).

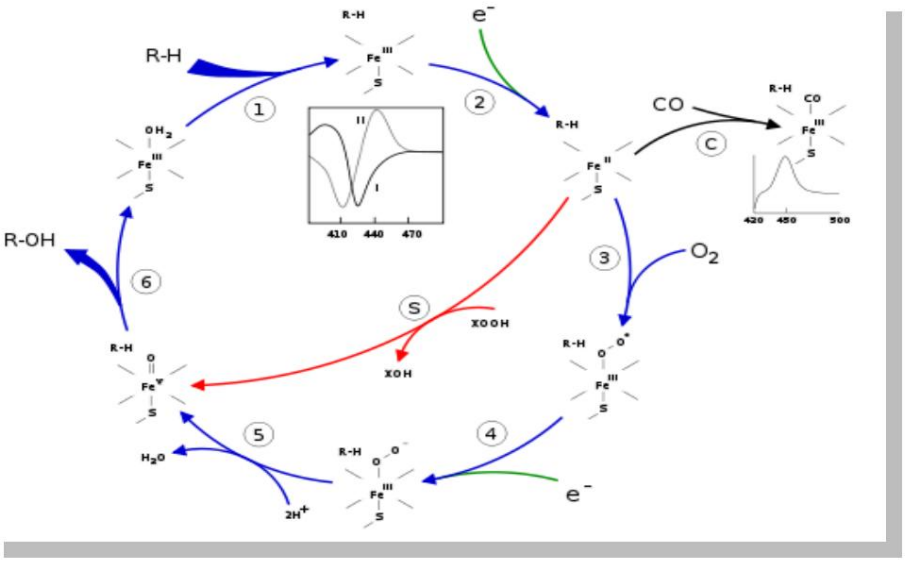


Figure n 18: Catalytic cycle of Cytochrome P450 (Meunier et al, 2004)

HYDROXYLATION

These reactions are very frequent; they correspond to the attachment of OH groups to linear chains or aromatic rings, thanks to microsomal hydroxylases.

Ex:

Valium —Hydroxylase→ Oxazepam (toxic drug)

Pentobarbital Hydroxylase Propranolol (renal elimination)

N AND S OXIDATION

They result in the attachment of an oxygenated function to nitrogen atoms or Sulfur example of N oxidation: sulfamides are transformed by the N oxidase enzyme into N hydroxylated derivatives which have a methemoglobinizing potential.

OXIDATIVE DESALKYLATIONS

These are reactions that detach alkyl radicals (most often **ÿCH3)** from oxygen or nitrogen atoms, we speak of O-dealkylation and N-dealkylation, this the latter leads to NOR (Nitrogen Ohne Radical) derivatives.

OXIDATIVE DEAMINATIONS

These reactions involve the detachment of amine groups (NH2) with the attachment of an oxygenated function. These reactions occur outside of hepatic microsomes.

thanks to monoamine oxidase (MAO) and diamine oxidase (DAO) located in the mitochondria of the liver, kidney and nervous system

OXIDATIVE DESULFURATION

They substitute sulfur atoms with oxygen atoms.

OXIDATIONS OF ALCOHOLS AND ALDEHYDES

They occur outside of hepatic microsomes thanks to alcohol-Dehydrogenases and aldehyde dehydrogenases located in the cytochrome of the hepatocyte

III.6.2.2.REDUCTION REACTIONS

These reactions are less significant than oxidations. They occur primarily at the hepatic level. Reduction reactions are those that attack ketone groups, disulfides and nitrate groups.

Example: Reduction of Cortisone (Adrenal Corticosteroid Hormone) to Hydro cortisol (Cortisol) under the effect of Reductase

III.6.2.3.HYDROLYSIS REACTIONS

These reactions take place in the liver but also in the digestive tract, plasma and In the lungs, the main enzymes are esterases and aidasses.

Example 1: Ester $\xrightarrow{\text{Esterase}}$ Acid and alcohol

Example 2: Procaine (Local Anesthetic) $\xrightarrow{\text{Esterase}}$ Para-Aminobenzoic Acid +Diethylaminoethanol

Ex3:

Acetylsalicylic acid ASPIRIN (INN) $\xrightarrow{\text{Esterase}}$ Salicylic Acid + Acetic Acid

***The metabolites formed by the phase I reactions have hydroxyl (OH), amino (NH2), or carboxyl (COOH) functional groups , which can be then conjugated to other molecules by type II reaction.

III.6.3. PHASE II REACTIONS

Phase II reactions often result in biologically active metabolites.
inactive, even more water-soluble and more easily eliminated by the kidneys or bile.

Conjugations are synthetic reactions between an exogenous substance or
its metabolite and a physiological molecule.

These reactions are catalyzed by transferase enzymes, which involve the addition of a gluconic acid molecule, sulfate groups, methyl groups, or acetyl groups to the active ingredient molecule or one of its metabolites. This is referred to as
glucurono-conjugation, sulfo-conjugation, methylation, acetylation.

III.6.3.1.GLUCURONOCONJUGATION

It consists of the conjugation of a fat-soluble, slightly polar xenobiotic with glucuronic acid, which is involved in the form of uridine diphosphoglucuronic acid (UDPGA).

An ether or thioether bond is established between the two compounds. A glucurono-transferase catalyzes the reaction.

Xenobiotics involved in glucuronidation are compounds
possessing: An **OH, COOH, NH2, SH function.**

Note : The cat appears to have limited glucuronidation capabilities.

III.6.3.2. SULPHOCUM CONJUGATION

This is a conjugation reaction of xenobiotics with sulfate ions.
previously activated in the form of phosphoadenosine phosphosulfate (PAPS), it involves a sulfotransferase.

The xenobiotics of interest are those possessing: An -OH function (Phenols, Alcohols), An -NH2 function (Aromatic amines).

Since the level of sulfates in the body is limited, these reactions are secondary.
compared to glucuronidation.

Note: Pork and fish are deficient in sulfonation.

III.6.3.3.METHYLATION

It consists of the attachment of a methyl group provided by activated methionine in the form of S-adenosylmethionine. The reaction is catalyzed by a methyl transferase.

The substrate can be: an -OH group (Phenols), certain unsaturated nitrogen heterocycles (Pyridine, Quinoline), or certain metals (Arsenic, Mercury). Mercury is thus seen Its toxicity increases due to the improved lipophilicity of methylmercury.

Example : **Serotonin methylation,** Location: **Brain cell,** Coenzyme: **S-adenosylmethionine**

Metabolite: **Melatonin.**

III.6.3.4. ACETYLATION

This is a reaction involving the fixation of an acetyl radical, which occurs in the form of acetyl-coenzyme A. An N-acetyltransferase catalyzes the reaction. Xenobiotics Those of interest are those possessing an aromatic -NH2 function, such as sulfonamides, which Acetylated compounds become **less water-soluble** and precipitate in the renal tubules, causing **nephropathy.**

Example : **Acetylation of Salicylic Acid**

Location: **Hepatocyte**

Enzyme: **Acetylase**

Metabolite: **Acetylsalicylic acid**

III.6.3.5. CONJUGATION WITH AMINO ACIDS

It exhibits a species-specific characteristic. It is produced using ornithine in **birds.** whereas glycyl conjugation is common in **mammals.**

Glycine, through its amine group, can amidate acids. The enzyme catalyzing the reaction is glycine N-acylase. The substrates are compounds with a specific function. **carboxylic** aliphatic or aromatic (benzoic acid, salicylic acid).

III.6.3.6.MERCAPTO-CONJUGATION

Mercapto-conjugation consists of conjugation with glutathione (tripeptide glutamyl-cysteinyl-glycine).

In fact, the complex formed is easily degraded, then secondarily acetylated to mercapturic acid. This is a very important detoxification reaction of polycyclic aromatic hydrocarbon epoxides and highly reactive free radicals.

III.6.3.7. TRANS-SULFURATION

Trans-sulfuration involves a **sulfur transferase** (formerly called "rhodanese"). This reaction is especially important in the detoxification of **cyanide ions -CN-** supplied by food; these ions are thus converted into thiocyanates SCN- in the presence of thiosulfate ions S2O3.

III.6.4. CONSEQUENCES OF BIOTRANSFORMATIONS

All these metabolic processes eventually lead to the depletion of the enzymatic machinery of the hepatocyte or other cells, resulting in the appearance of pathologies and deficiencies (e.g., liver cirrhosis, which develops in alcoholics and...).
drug addicts).

If the absorbed substance is an inactive drug that will be metabolized into a The active compound is called a prodrug. These reactions can also lead to the formation of so-called "reactive" metabolites, which can be toxic. These reactive metabolites are normally reduced ("detoxified") in the presence of glutathione.
the quantity of which is limited at the liver level.

When the glutathione store is depleted, these reactive metabolites can induce DRUG-INDUCED CYTOLYTIC HEPATITIS.

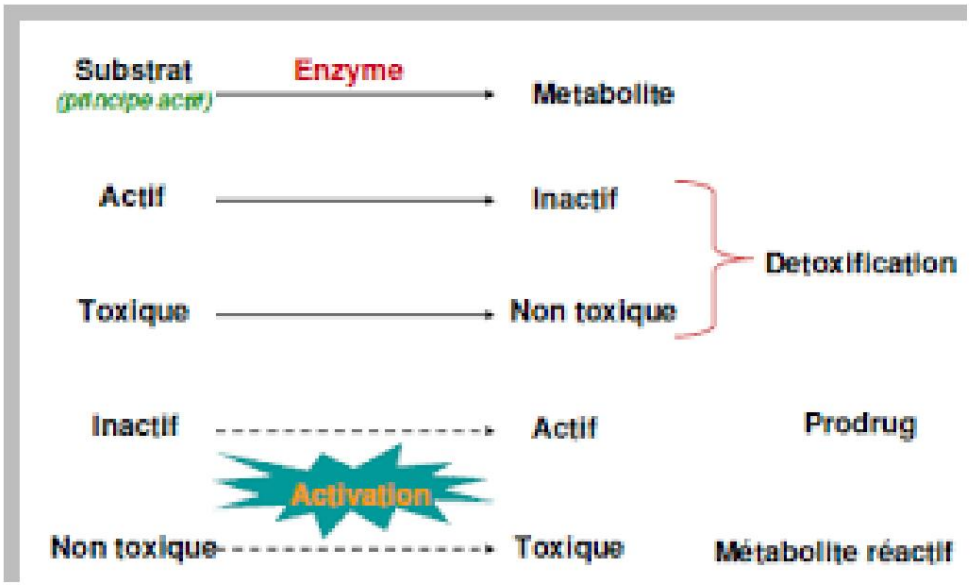


Figure 19: Consequences of Biotransformations of a Drug (Bendouadi, 2020)

III.6.5. CHANGES IN CYP450 ENZYME ACTIVITY

- **Increased enzymatic activity**

It is caused by inducing substances, increasing the synthesis and activity of CYPs, certain medications, especially anti-infectives and anticonvulsants, St. John's wort (both a plant and a medicine), tobacco, alcohol

- **Decreased enzyme activity**

It is caused by inhibitory substances, primarily medications:
azole antifungals, certain macrolides, protease inhibitors, antagonists of bradycardic calcium channels, grapefruit (juice or fruit).

III.6.5.1. ENZYMATIC INDUCTION

When certain medications are used for prolonged and repeated periods, a reaction of the body is sometimes observed, resulting in a progressive decrease in the pharmacological effects of that medication.

This phenomenon has been demonstrated with barbiturates. Repeated administration of identical doses of a barbiturate, for example phenobarbital, induces the synthesis of CYP3A and CYP2B6 and leads to a decrease in the duration of narcosis.
(sleep).

- **Chronic administration** of a substance may stimulating its own biotransformation **(auto-induction) :** the case of carbamazepine, Tegretol®, or the biotransformation of another substance **(hetero-induction) :** the case of phenytoin, Epanutin® which induces the metabolism of acenocoumarol, Sintrom ® .

Inducers can be drugs or environmental pollutants (herbicides, pesticides). Xenobiotic-inducible enzyme systems include cytochrome P450s, glutathione-S-transferases, glucuronyl-transferases.

Certain substrates, enzyme inducers, are capable of increasing **the** synthesis of cytochromes P450 and consequently their enzymatic activity and therefore the elimination of drugs, which reduces their time in the body.

The inducing effect is not very specific. An inducer can increase synthesis and the enzymatic activity of one or more isoforms of CYP.

EXP: rifampicin is an inducer of CYP 3A4 and 2C19.

Induction time and duration:

The maximum inducing effect is obtained after several days of treatment by The inducer: maximum effect in 10 to 15 days

III.6.5.2. ENZYMATIC INHIBITION

This is the opposite phenomenon of enzyme induction. It is most active often at the level of a single CYP and schematically responds to two mechanisms:

* Irreversible inactivation of CYP by the inhibitor.
* Competition at the level of the same CYP between two substances:
  - Administered simultaneously.
  - Fixed and metabolized by the same CYP.

Depending on their affinity for an enzyme, some drugs will inhibit the metabolism of drugs with lower affinity or those present in lower concentration.

Some xenobiotics inhibit biotransformation enzymes, particularly those involved in microsomal oxidation. This is an immediate phenomenon that can last
for several days or even several weeks

This enzymatic inhibition must be taken into account in therapies combining several drugs. Reducing the inactivation of an active ingredient risks causing toxicity. By slowing down the

metabolism of certain drugs, by increasing their concentrations
Plasma levels increase the risk of adverse effects, sometimes with serious consequences. serious.

Piperonyl butoxide, which lacks antiparasitic activity, is combined with pyrethrins. to protect them from oxidative metabolism and prolong their biological action.

Inhibition of cytochrome P450 by certain drugs or foods known as
Enzyme inhibitors are another factor in metabolic variation.

Inhibition is most often competitive and manifests rapidly with the most often an increase in plasma concentration and prolongation of the effect pharmacological and the half-life of the drug whose metabolism has been inhibited with a risk of toxicity.
Enzyme inhibition is frequently the cause of drug interactions.

III.6.6. FACTORS OF VARIATION

*** Many factors modify biotransformation reactions:

Intrinsic, biological factors:

- Genetic factors (species, breed, individual).
- Pathophysiological factors (Age, Sex, Genetics, Nutrition, Pathology and therapy).

Extrinsic factors related to the medication or other associated factors:

- Chemical variation, dosage.
- Enzyme induction and inhibition.

III.7. ELIMINATION- EXCRETION (PK4)

GOALS

- Define total clearance and that of a specific organ, particularly the kidney
- Explain the mechanisms of hepatic and renal elimination
- Explain the influence of the physicochemical characteristics of the drug and the pH on renal elimination

III.7.1. DEFINITIONS

Any substance introduced into the body must be eliminated to a greater or lesser extent. rapidly, unless it binds irreversibly to tissues that could become toxic at some point during the fourth cycle. Example: the accumulation of pesticides in birds migratory.

Elimination involves general transmembrane processes: passive diffusion, filtration, and active transport. Numerous therapeutic and toxicological consequences are considered.

Once they have completed their journey through the body, xenobiotics are eliminated. in unchanged form or as metabolites after biotransformation.

The process of eliminating a drug encompasses the phenomena of excretion. (essentially: from a quantitative, renal, and biliary point of view) and metabolism. However, there are other elimination routes, among which the mammary route takes on particular importance in veterinary medicine in connection with residues of xenobiotics in milk.

The parameter that allows us to quantify the elimination process is clearance.

III.7.2. CONCEPT OF CLEARANCE

This is the parameter that allows us to quantify the elimination process.

This is the volume of blood that is filtered and cleared per unit of time (clearance is measured in units of flow rate, for example, ml/min). We distinguish between:

ÿ Hepatic or biliary clearance.

ÿ Renal clearance.

ÿ Plasma (or total) clearance.

Plasma clearance is defined as the volume of plasma that is completely cleared.
of the drug per unit of time.

The clearance of an organ corresponds to the amount of blood that passes through that organ.
and which will be completely cleared of the drug per unit of time. It is equal to the product of the blood flow rate in the organ and the organ's extraction coefficient:

Cl = Q x E

Where Cl = clearance, Q = blood flow rate, and E = extraction coefficient
The extraction coefficient is calculated as follows: **E = (CA – CV)/ CA**

Where: CA is the concentration of the drug at the organ's entry point,
CV is the concentration of the drug at the organ exit.

III.7.3. CONCEPT OF PLASMA HALF-LIFE (T½)

Time required for the plasma concentration to decrease by half. The half-life is not solely a reflection of drug elimination but a criterion
composite related to its distribution and elimination.

Knowing the half-life allows us to predict the frequency of administration of the medication (number of daily doses) to obtain the plasma concentration
desired.

A half-life is a constant; it means that regardless of the concentration at
which one we are considering; if we decrease this concentration by 50%, we will have the same time period.
time between Cmax and 50% of Cmax.

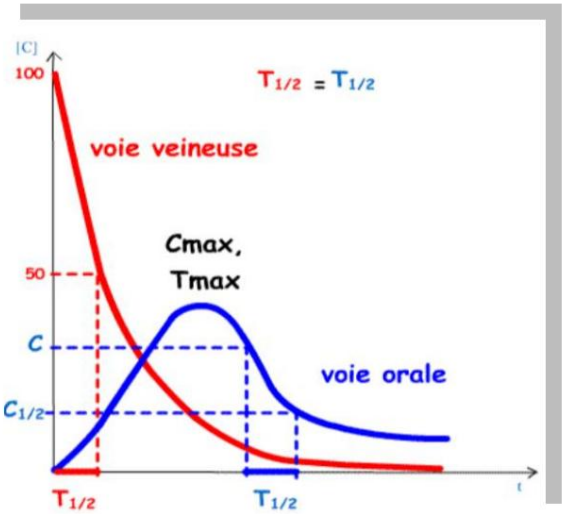


Figure 20: Plasma half-life of a drug administered intravenously and orally (Lamand, 2010)

III.7.4. MAIN METHODS OF ELIMINATION

The excretion of an active ingredient can occur through all the body's fluid elimination pathways: urine, bile, gastrointestinal secretions, saliva, etc.
sweat, breast milk, lungs (for volatile substances).

The two main routes of elimination are the renal route and the biliary route.

III.7.4.1. RENAL ELIMINATION

The kidney, which receives a quarter of the cardiac output, eliminates drugs such as various other substances in the body. From a physiological point of view, the nephron, the basic unit of the kidney, acts through three different mechanisms: glomerular filtration, secretion and tubular reabsorption.

a) Glomerular filtration

The vast majority of chemical substances (small size, water-soluble) are passively filtered at the level of the glomeruli, through the numerous membrane pores of the blood capillaries. The form bound to plasma proteins will therefore not be filtered and remains in the circulating fluid; only the free part is suitable for glomerular filtration, which explains the longer duration of action of drugs with high protein binding.

Regardless of the degree of lipophilicity and the degree of ionization, filtration occurs. provided that the molecular size is filterable (less than 68,000 Daltons).

In humans, a volume of 120 ml/min is filtered, resulting in the formation of the primary urine. This is what is called **"glomerular clearance",** it expresses the volume filtered per unit of time.

b) Tubular secretion

Proximal convoluted tubule cells are capable of actively excreting substances dissolved in the plasma into the urine (2 systems: acids and **bases).** This Secretion occurs against the concentration gradient; it is saturable. Two Substances can compete for the same active transport system, so one drug can alter the elimination of another and even cause its accumulation and therefore toxicity.

This active pathway results in the formation of secondary urine.

c) Tubular reabsorption

Tubular reabsorption occurs throughout the nephron. It can take place on the filtered volume only, or on the filtered and secreted volume. It is rarely active. Many endogenous substances are reabsorbed at this level, such as: glucose, amino acids, vitamins, Na+ , Ca++, K+,

Most often, this involves the **passive** diffusion of a molecule from the tubular lumen into the blood. This reabsorption occurs depending on:

- **Urine/plasma concentration gradient of the substance:** it is necessary that the concentration of the reabsorbed molecule is greater in the urine than in the plasma.
- **Degree of ionization of the drug:** only the non-ionized fraction is reabsorbed.

For ionizable fat-soluble compounds, reabsorption depends on the differences pH difference between urine and plasma.

The pH of urine varies depending on the animal species and diet. food.

- **Degree of solubility of the substance:** water-soluble, ionized molecules are not not reabsorbed and are eliminated in the urine. Conversely, lipid-soluble substances diffuse easily through the tubular epithelium according to the gradient of urine/plasma concentration.

- **Urine pH:** in acidic urine, an acidic active ingredient is reabsorbed and therefore less eliminated, and the opposite is true for basic active ingredients.

This explains the longer persistence of weak acids such as sulfonamides or acetylsalicylic acid in carnivores (their urine tends to be acidic) compared to herbivores whose urine is on average alkaline. Furthermore, in cases of poisoning by these compounds.

It would be beneficial to alkalize the urine by administering bicarbonate intravenously. sodium, which will promote elimination.

*** At this stage, the final urine is formed, which is generally more concentrated than primary urine.

- In carnivores, this pH is 5.5 to 7.0, in herbivores 7.3 to 7.6, and in omnivores from 5 to 7.5.

Excretion rate = Filtration rate + Secretion rate - Rate of reabsorption

The excretion rate of an active ingredient determines its renal clearance and by consequently its half-life.

d) **Variation in renal elimination**

- The processes of glomerular filtration and tubular secretion only reach their full development two days after birth in calves, 3 and 7 days in lambs and kids, and on the 10th day in piglets.
- Glomerular filtration is approximately 2 times lower than in adult animals.
- In cases of kidney failure, there is a decrease in urinary elimination of xenobiotics.
- For this reason, administrations must be spaced out or medications administered that can be eliminated by other means.

III.7.4.2. BILE ELIMINATION

Biliary excretion of substances metabolized by the liver requires normal physiological function. This pathway is similar to that of the
Renal tubular secretion, this transport process is saturable and can be used by
another substance that requires the same transporter; this is called hepatic clearance

or biliary, the drug is conjugated and released into the intestinal lumen; it can enter enter an enterohepatic cycle.

ÿ **The enterohepatic circulation**

The process by which a drug eliminated via the bile can be reabsorbed upon arrival in the duodenum and re-enter the general circulation. This phenomenon
intervenes for active ingredients that have biliary excretion.

After the first pass through the liver, the molecule can be metabolized and after transformation into a conjugated derivative in the form of glucuronides, it is eliminated by biliary.

In the duodenum, conjugated metabolites can be hydrolyzed by a glucuronidase from digestive bacteria, returning the initial molecule which is then reabsorbed in the intestinal mucosa, and via the portal system, it
passes back into the liver and then into the general circulation, thus a portion of the active ingredient can be redistributed throughout the body.

This recycling leads to an increase in plasma concentrations and the duration of the active ingredient's residence in the body, and therefore a delayed effect often exploited in therapeutic.

Many medications exhibit persistent enterohepatic recirculation; this is exploited in specific treatments of the digestive tract. Example: Douvicides (treatment of
parasites of the bile ducts).

III.7.4.3. SALIVA ELIMINATION

It is not considered an important route of excretion, because elimination
the amount of the active ingredient is not quantitatively significant.

The transfer to saliva occurs via passive diffusion from the plasma. This depends on the lipid solubility of the compound, its degree of ionization in the blood, as well as the pH and salivary flow rate.

This is a method used in some treatments of the oropharyngeal sphere.

- Slightly alkaline (pH ÿ8.0 - 8.4) in ruminants, 100 to 190 liters /day.
- Neutral in horses (pH ÿ 7.3 - 7.6), 10 to 12 liters.
- Rather acidic in carnivores and humans (pH ÿ 6.5 - 7.2), 0.5 l.

III.7.4.4. ELIMINATION VIA THE DIGESTIVE MUCUS

Apart from biliary and salivary elimination, xenobiotics can be directly excreted by stomach and intestinal cells by simple diffusion.

Given the acidic pH of the stomach and duodenum compared to blood pH, only basic xenobiotics are affected due to the phenomenon of ion trapping.

which are likely to be excreted in this way

This process is of fairly limited importance except in ruminants due to the considerable relative mass of the stomachs.

III.7.4.5. LACTIC OR BREAST ELIMINATION

Milk elimination is very important in therapeutics when choosing... treatments for mastitis and when the lactiferous route is not possible or during associated treatments.

Milk is slightly more acidic than plasma: in goats and cows, it is typically from 6.5 to 6.8. In mastitis, it can approach blood pH.

Basic substances in the blood plasma pass easily into breast milk, resulting in quickly to high concentrations.

Acidic compounds diffuse very weakly from the blood into the milk and are unable to reach effective levels. However, this diffusion is never Completely useless.

In milk, xenobiotics can remain in a free state or bind to many supports which **reduces its ability** to reach the action sites.

Some anthelmintics (nitroxinil, rafoxanide) are largely eliminated by the milk, requiring relatively long waiting times **(economic disadvantage).**

The waiting time is the time that elapses between the last administration therapeutics and the marketing of foodstuffs of animal origin of a good safety, with no danger to the consumer.

Blood reabsorption from milk following extra-mammary diffusion constitutes the second route of elimination of compounds administered via the galactophore. It is the fat-soluble compounds that are thus eliminated from the udder by diffusion passive.

III.7.4.6. ELIMINATION VIA EGGS

The presence of xenobiotics in eggs is related to the physiology of egg formation in the ovary and to the respective sites of yolk synthesis.
(liver) and albumen (oviduct).

Fat-soluble drugs persist in the yolk even after treatment is stopped, until all infected oocytes in the ovary are eliminated.

The production of an egg, particularly the yolk, takes several days, resulting in a lag of nearly a week between plasma concentrations and egg levels. Consequently, implementing [the following] is practically difficult.
therapeutic treatments in laying hen farming, due to the waiting periods that must be respected.

III.7.4.7. PULMONARY ELIMINATION

Despite its rich vascularization, its exchange surface area and its equipment Enzymatically, the lung is not considered an organ of absolute elimination because only volatile and gaseous molecules undergo this mode of elimination, e.g., plant essences such as camphor, eucalyptol, thymol, and alcohols;
general anesthetics: fluothane and methoxy-fluorane, and expectorants: eucalyptol and guaiacol.

III.7.4.8. DISPOSAL BY SECONDARY TREATMENTS

The other elimination routes are of almost no therapeutic interest; excretion is observed through the nose, skin, sweat, tears, and...
skin appendages (nails, hair, claws, fur, teeth). These pathways are, without a doubt, very accessories for the disposal of medications that are found in trace amounts but may have therapeutic importance, particularly in the treatment
of microbial and parasitic infections. All these pathways rely on the affinity of molecules for tissues.

CONCLUSION

The study of the kinetics of a xenobiotic allows us to understand its fate in the organism based on data relating to the physicochemical properties of the substance on the one hand, and the anatomical and physiological characteristics of the animal species in question on the other. Its therapeutic and toxicological consequences are obvious.

• In therapeutics, the choice of drug by the veterinarian must be based on pharmacokinetic data involving the concepts of absorption, distribution,
biotransformation and elimination of the active ingredient.
The prescribed dosage must take into account the animal's liver and kidney function, as well as the simultaneous administration of other active ingredients.
In toxicology, knowledge of this pharmacokinetics is of twofold importance.
It allows the treatment to begin with its various objectives, namely limiting resorption, combating toxic effects and facilitating the elimination of the toxin.

It also allows us to know the levels of residues in food products
animal-based foods are the basis for setting withdrawal times in order to put
providing consumers with products that present no danger.

CHAPTER IV

PHARMACODYNAMICS

GOALS

- Identify the main types of receptors for mediators.
- To understand the mechanisms of action of a drug on a receptor.
- List the factors that affect the action of the drug.

IV.1. DEFINITIONS

Pharmacodynamics is defined by the mode of action of drugs, which translated by the desired clinical effects.

This clinical effect is explained by the different biochemical steps induced by the active ingredient molecule and its interaction with the enzymatic and molecular mechanisms of the body.

The term active substance, or active ingredient, refers to the chemical substance that, in a drug (understood as a pharmaceutical product), possesses a pharmacological effect. However, the effect of most drugs results from their interactions with the "Receptors".

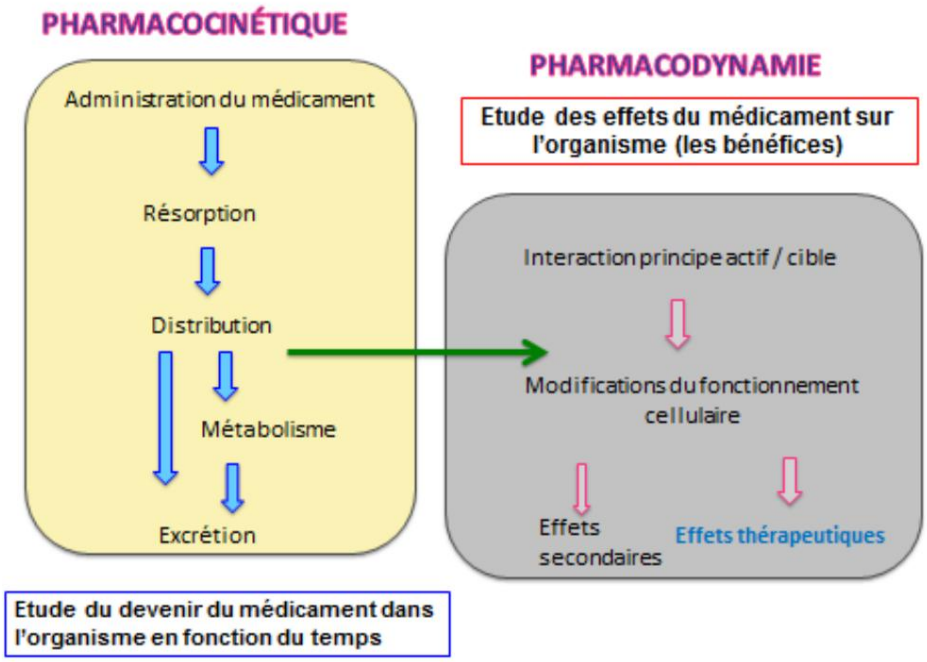


Figure 21: Interactions of the body with the drug and the drug with the body (Bousquet-Mélou, 2014

Definition of a drug (drug, medicine, medication)

“ Any substance or composition presented as having **curative or preventive** properties with regard to human or animal diseases, as well as any product administered to humans or animals for the purpose of establishing a medical diagnosis, restoring, to correct or modify their organic functions.”

The action of an active ingredient depends on the dose; the "dose-effect" relationship reflects this. pharmacodynamic power.

The intensity of the clinical effect depends on both the dose and the time of action of the molecule, and therefore on its plasma concentration, which itself depends on its distribution and elimination, and thus on its pharmacokinetics; this is what is called the time of "Half-life" of a drug in the body.

IV.2. MECHANISMS OF ACTION OF A DRUG

Mechanisms of action

- **Non-specific actions: physico-chemical properties**
  - Gastric and intestinal dressings
  - Acid-base balance modifiers
  - Osmotic balance modifiers (mannitol)
- **Specific actions: interactions with macromolecules**
  - **Lipids**
    - Amphotericin B: a surfactant with antifungal properties
  - **Nucleic acids**
    - Anticancer agents, steroids
  - **Proteins:**

    Receptors, ion channels, enzymes, transporters

Other classifications are available:

- Physico-chemical action.
- Substitute action.
- Interaction with the metabolism of an endogenous substance.
- Interaction with microorganisms.
- Interaction with DNA.
- Action on the phenomenon of ion transport.
- Interaction with the targets of endogenous substances.

IV.3. TARGET OF SUBSTANCES

A drug is a molecule from which an action can be expected.
pharmacological action at the level of target tissues. This molecule is often an exact copy of a neurotransmitter or a natural hormone whose action it is supposed to mimic. The reproduce the action in the organism · action sometimes stems from a simple property. Chemically, the active molecule reacts with a molecular entity, the RECEPTOR. The old concept: (corpora non agunt nisi fixata):
(Medicinal substances do not work if they are not bound).

The pharmacological action triggers a sequence of cellular events that we can be described as a therapeutic effect.

M+R MR = pharmacodynamic action

The action of an active ingredient depends on the dose, the "Dose-effect" relationship, reflecting pharmacodynamic power.

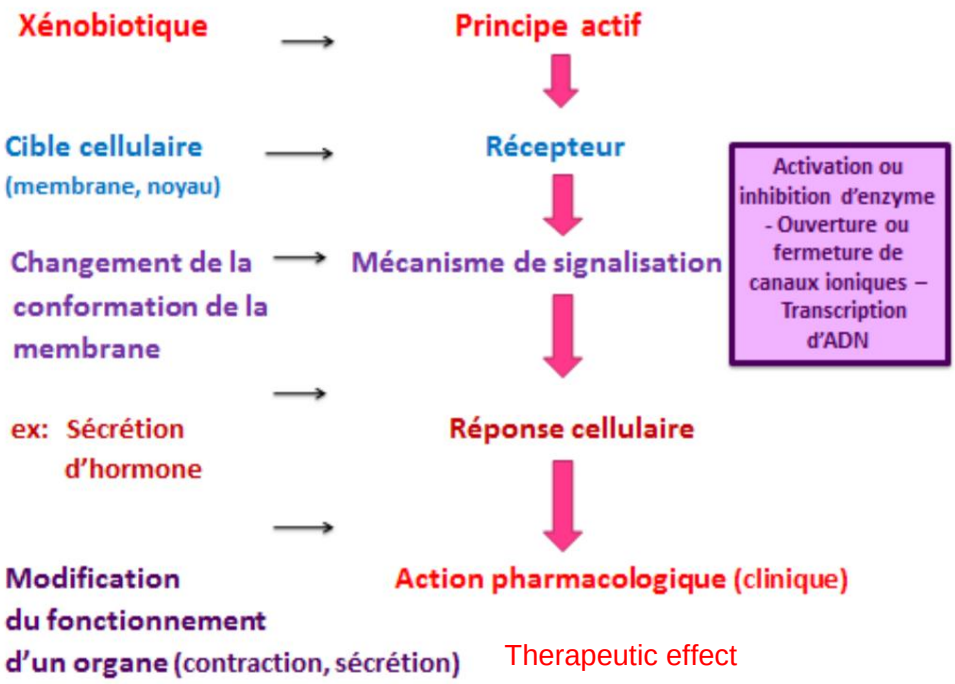


Figure n°22: example of a target of action such as ion channels (Bensegueni Tounsi, 2014).

- **The desired effect of a treatment, the one for which the drug was intended designed and marketed**

• " immediate measurable improvement or delayed, transient Or definitive, of the state health and well-being of a subject of the or in relationship with the use of a drug and its pharmacological has a priori, explainable by one or properties several of ».

Side effects

• Inevitable non-therapeutic side effects occur at normal doses in the majority of patients

e.g., antihistamines cause drowsiness.

Side effects

• Unpredictable side effects appear at normal doses in some patients.

e.g., isoniazid hepatotoxicity.

Toxic effects

• Inevitable side effects appear during an overdose, e.g., hepatotoxicity of the paracetamol.

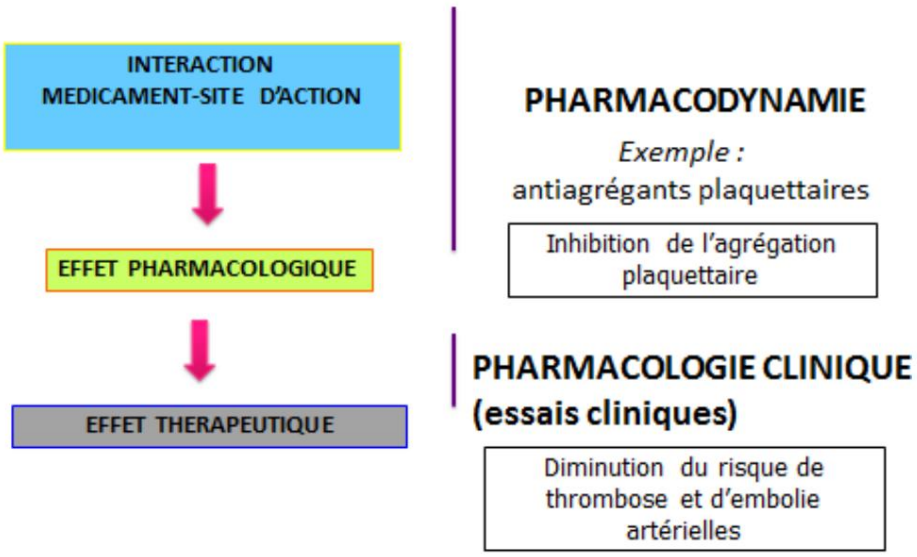


Figure 23: Pharmacological effect and therapeutic effect (Bousquet-Mélou A, 2014)

• The intensity of the clinical effect depends on both the dose and the duration of action of the molecule,

Therefore, its plasma concentration, which itself depends on its distribution and of its elimination, therefore of its pharmacokinetics; this is what is called time of **"Half-life"** of a drug in the body.

IV.4. CONCEPT OF HALF-LIFE

The half-life of a drug is the time required for the maximum plasma concentration of the active ingredient to decrease by half compared to its
Initial concentration. This ultimately allows us to assess the volume of distribution of this active ingredient and its elimination rate, expressed by the duration of action and the persistence of the clinical effect. If the half-life of the active ingredient is **long,** the drug has a **delayed effect.**

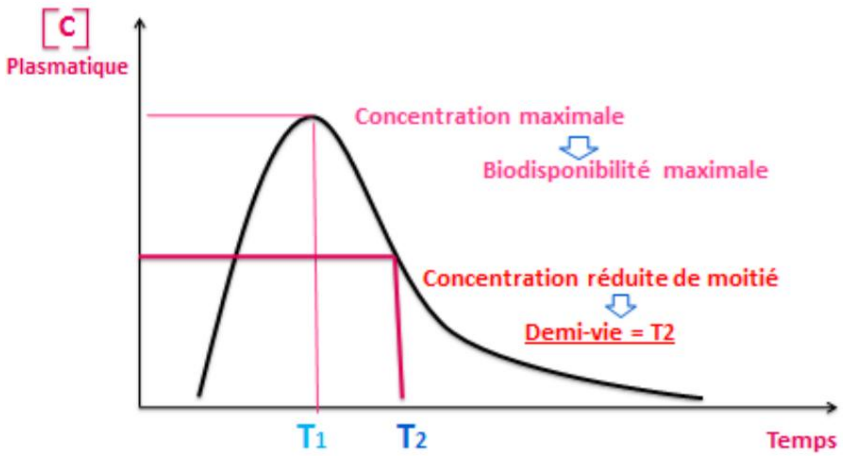


Figure 24: Maximum Bioavailability and Half-Life

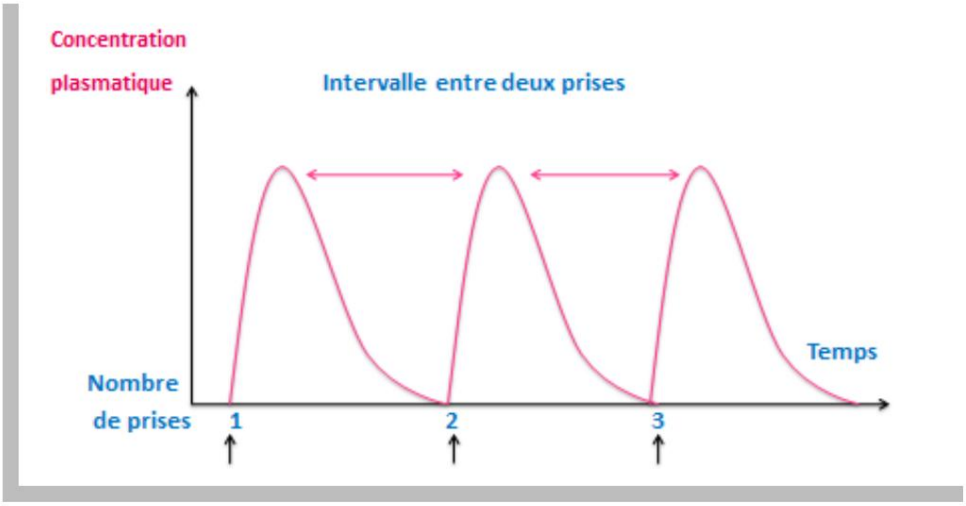


Figure 25: Half-life determines dose repeatability (Bensegueni Tounsi, 2014)

IV.5. CONCEPT OF RECEPTORS

After circulating in the body, a drug arrives at the sites receptors where it exerts a biological response.

Receptors are by definition membrane or intracellular proteins capable of recognizing and binding, most often specifically, "Mediators". or "ligands" which are endogenous and exogenous (xenobiotic) molecules.

- Neurotransmitters, or neuromediators, are chemical compounds released by neurons that act on other neurons, called postsynaptic neurons, or, more rarely, on other types of cells.

In biology, a ligand (from the Latin ligandum, binder) is a molecule that binds reversibly to a targeted macromolecule, protein or nucleic acid, playing a role in generally a functional role: structural stabilization, catalysis, modulation of an activity enzymatic, transmission of a signal.

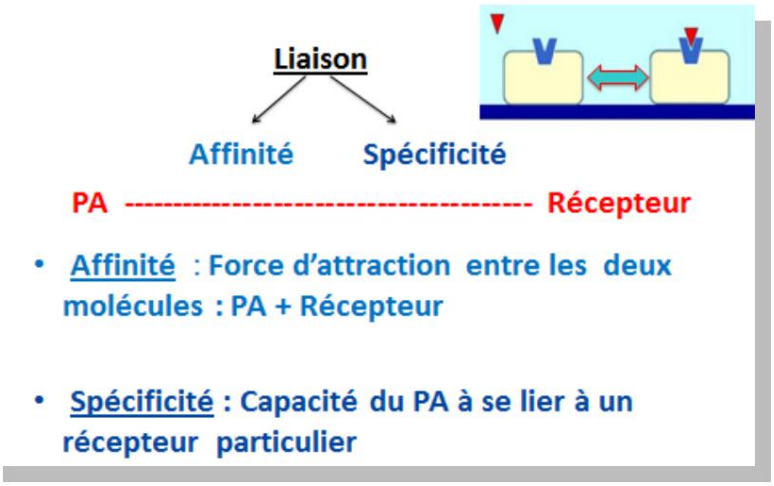


Figure 26: Binding of the active ingredient with its receptors (Landry and Gies, 2009)

The binding of the mediator triggers a biological response obtained by
via an amplifier and an effector (e.g., G protein).

Receptors are named after their usual ligand or mediator.
example: Adrenergic, GABAergic, morphine, nicotinic receptors.

ÿ The interaction of the drug with the receptor binding site, the force of attraction between the two molecules, is called "Affinity".

This affinity is explained by the number of molecular bonds (Covalent-
ionic (Van der Walls bonding) that can be established between the drug and its receptor.

ÿ The ability of drugs to bind to a particular type of receptor is
called "specificity".

The binding of the ligand to the receptor is a specific binding that triggers an effect biological or, conversely, blocks this effect. This binding is **saturable ,** whereas a binding to a non-specific site, such as a binding to plasma albumin, does not
It does not trigger a biological effect and is not saturable. The ligand-receptor binding is a reversible reaction.

ÿ Selective.

When receptor subtypes exist, an agonist is selective if it interacts
than with one of these subtypes (e.g., cardioselective ÿ-blocker). It is not absolute.

IV.5.1. DIFFERENT TYPES OF RECEPTORS

The receptors are located in two places in the cell: in the membrane cytoplasmic and in the cell nucleus.

ÿ **Membrane receptors**

ÿ **Direct binding with an effector** (channel or enzyme).

ÿ Channel receptors: ÿ Nicotinic insulin to acetylcholine.

Enzyme receptors: resistance (R) (tyrosine kinase activity).

ÿ **Indirect link with an effector**

ÿ G protein-coupled receptors: **Intracellular** R. muscarinic to acetylcholine.

ÿ **receptors** ÿ Transcription factor receptors.

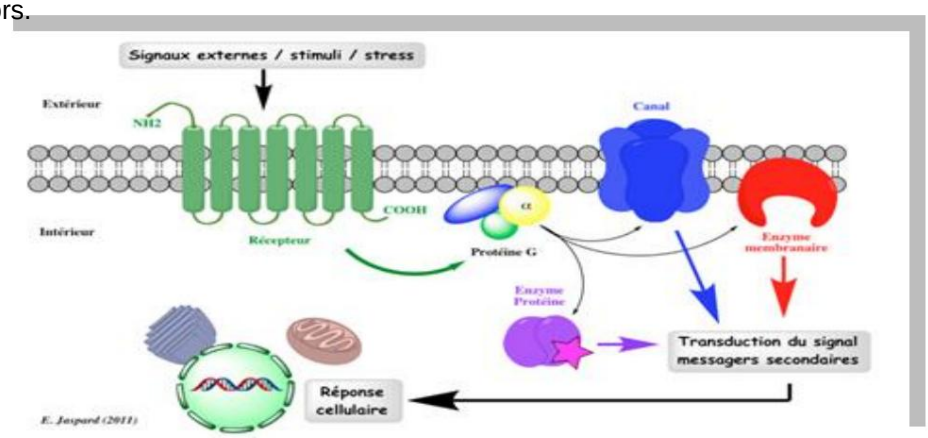


Figure 27: Different types of membrane receptors (Jaspard, 2012)

IV.5.1.1. IONIC CHANNEL RECEIVERS

These are polymeric receptors (made up of several subunits), they undergo a conformational change upon ligand binding, which opens a channel and allows the passage of ions.

- Ligand : (Fixation de la molécule du mdmt)
- Changement de la membrane
- Ouverture du canal Passage des ions
- Détachement du ligand
- Fermeture du canal

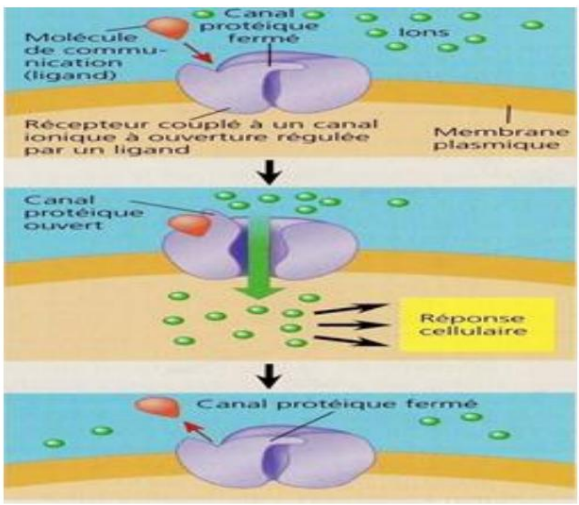


Figure 28: Ion channel receptor (Marieb, 2008)

Examples:

1) The **nicotinic acetylcholine receptor** at the motor endplate is an example of a ligand-activated ion channel. The receptor complex composed of 5 protein subunits, each containing four transmembrane domains. The opening of an ion channel with an influx of Na+ (and an efflux of K+) causes membrane depolarization and triggers a potential action.

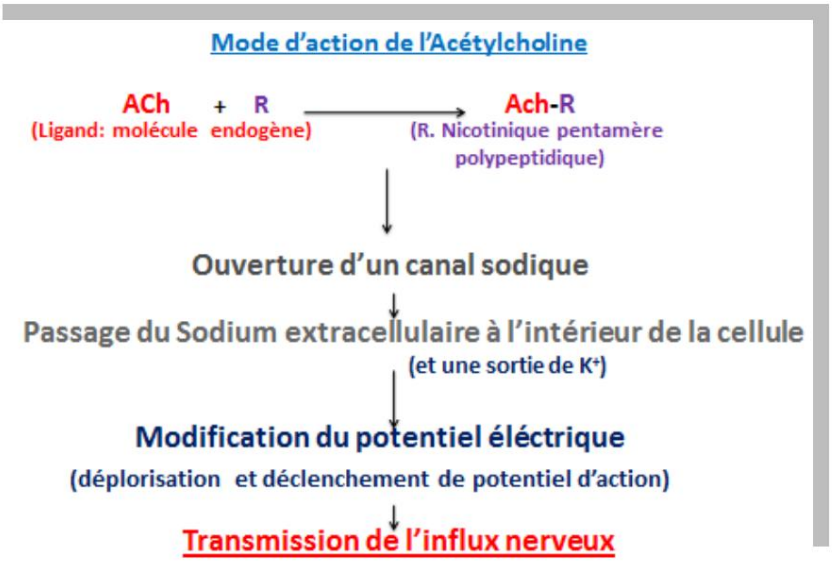


Figure 29: Nicotinic acetylcholine receptor (Bousquet-Mélou, 2019c)

2) The sodium channel receptor is an example of a receptor whose activity is regulated. by the variation of the membrane potential; it is present on **cell** membranes **excitable nerve and cardiac cells, and on muscle cells skeletal cells.** In these resting cells, the Na+ /K+ -ATPase pump maintains an intracellular Na+ concentration much lower than that of the extracellular environment. Membrane depolarization triggers the opening of the ion channel and a transient influx of Na+ ions , followed by an inactivation step and a return to the state of rest.

3) The **GABAergic receptor** for the ivermectin molecule (antiparasitic), allowing the opening of the chloride channels which causes paralysis of the parasite.

IV.5.1.2. RECEPTORS-ENZYMES

They combine, on the same cytoplasmic membrane protein, a receptor function (mediator binding) and an enzymatic function. The binding of the molecule the receptor modulates the activity of a given enzyme.

Example #1:

- **Hopostamine** (an antihistamine), which binds to and inhibits histidine decarboxylase, enzyme responsible for the decarboxylation of histidine into histamine and for triggering the allergic reaction.
- **An enzyme** is a protein biocatalyst capable of accelerating a reaction biochemical,

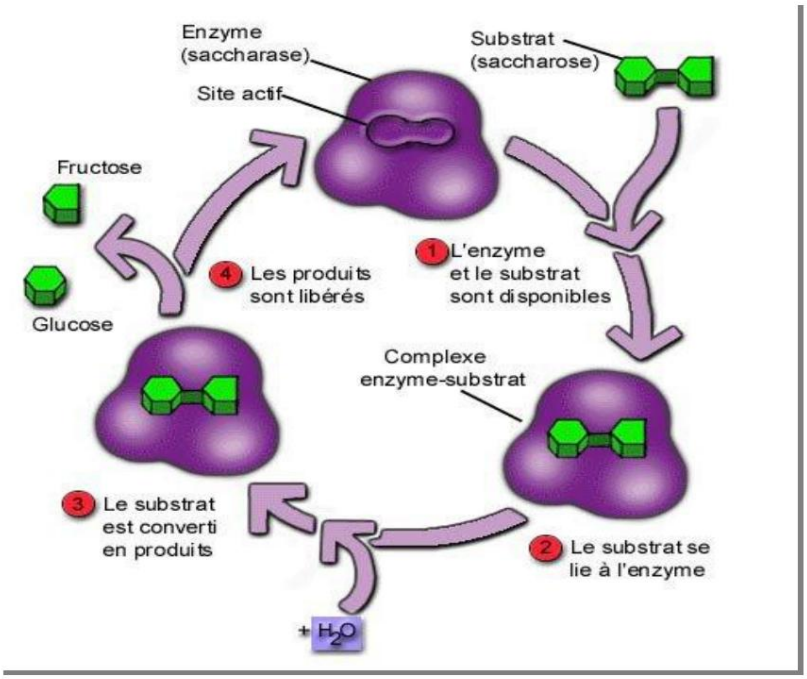


Figure 30: Receptors-enzymes (sucrase) (Campbell et al, 1999)

There are two (02) sites:

- Active site fixing the substrate

- Regulatory site binding biochemical compounds capable of controlling the action of the enzyme.

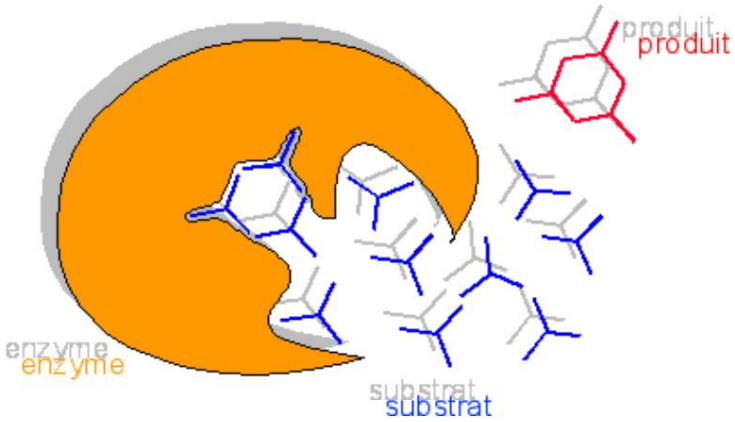
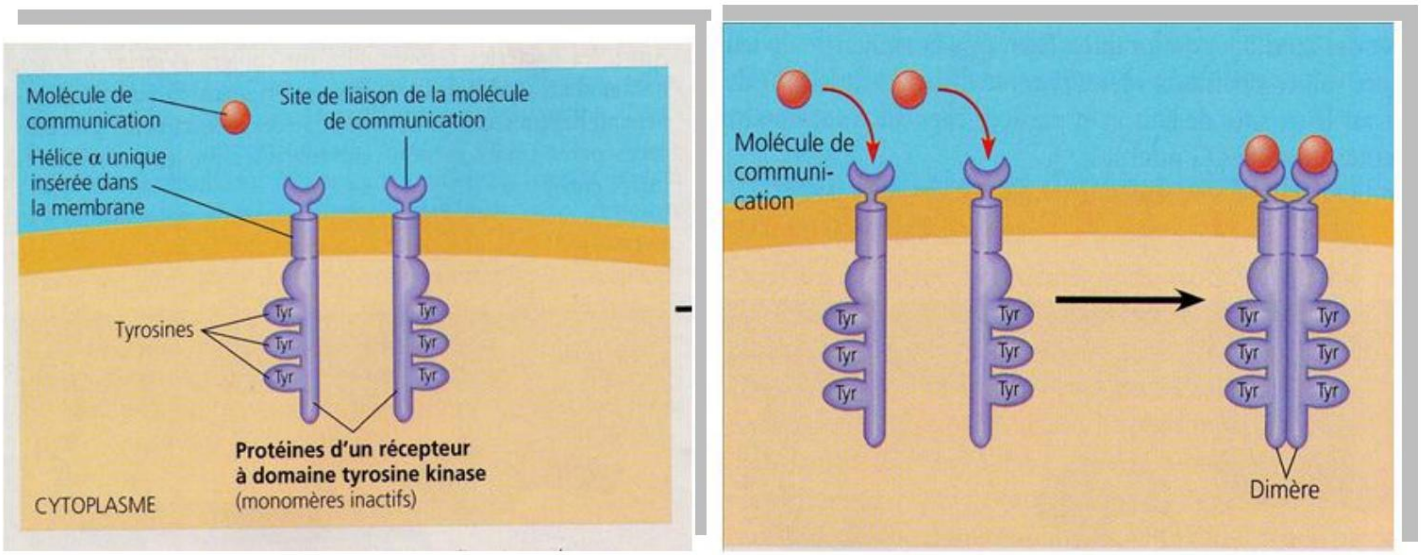


Figure 31: Degradation of the substrate by its enzyme (Danchin, 2023)

Example #2:

The insulin receptor is an enzyme activated by a ligand. When insulin binds to the extracellular binding site, a tyrosine kinase activity in the part The intracellular receptor is activated. Protein phosphorylation triggers a modification of cellular functions:

- Activation of the membrane protein that captures and transports blood glucose to inside the cell (Cellular response).
- Activation of intracellular proteins involved in glycogen synthesis metabolism (Metabolic response). And - Drop in blood glucose (Clinical response).



a: Protein of an inactive receptor

b: binding to the molecule's site

c: Activated Tyrosine

d: activated intermediaries

Figure 32: Receptor enzyme with tyrosine kinase domains (Campbell and Reece, 2008)

IV.5.1.3. G PROTEIN COUPLED RECEPTORS

These receptors consist of a helical chain of amino acids organized into seven segments. The seven transmembrane segments are presumably arranged in a circle containing a cavity and a site at its center.

binding for the signal molecule.

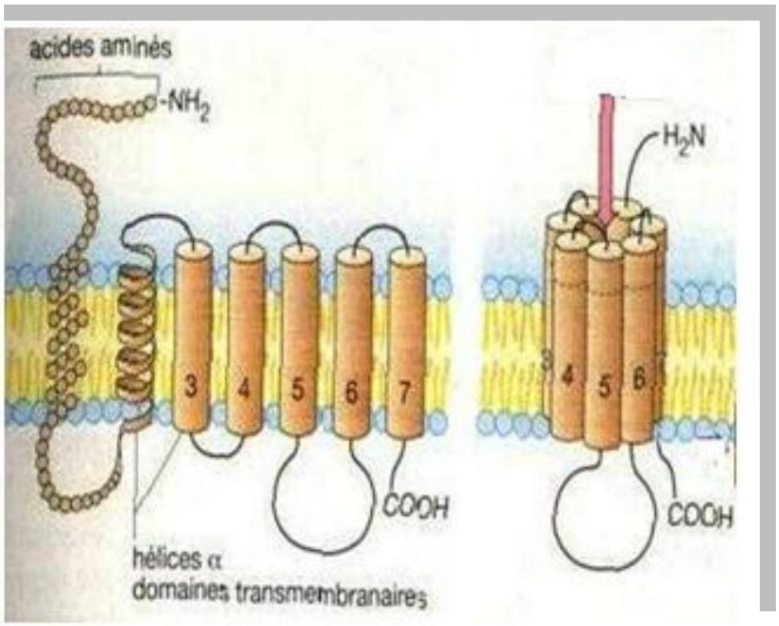


Figure 33: Receiver in the form of a helix (Lüllmann et al, 2010)

The association of the ligand, or a pharmacological analogue possessing activity agonist, induces a conformational change in the receptor and allows it to enter contact with a G protein (guanylic nucleotide binding protein).

G proteins are located on the inner surface of the plasma membrane and are formed of three subunits: alpha, Beta and Gama.

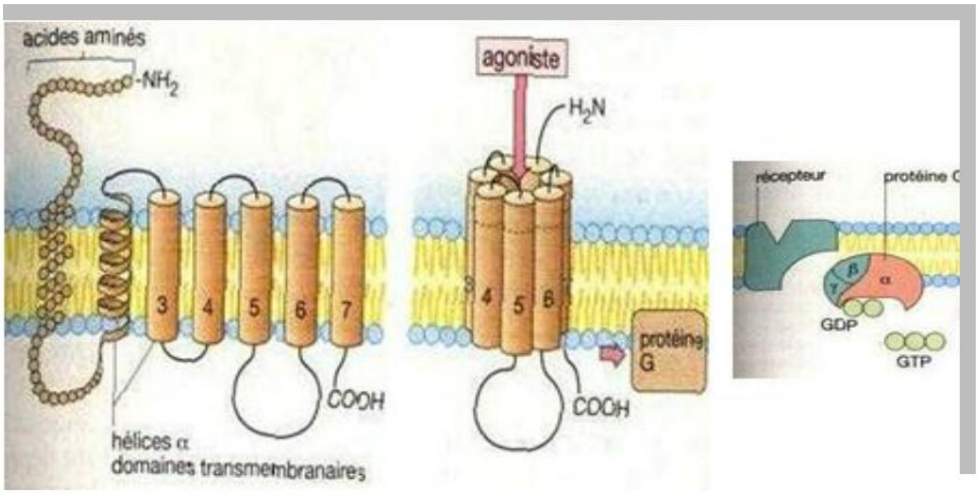


Figure 34: G protein and its three subunits (Lüllmann et al, 2010)

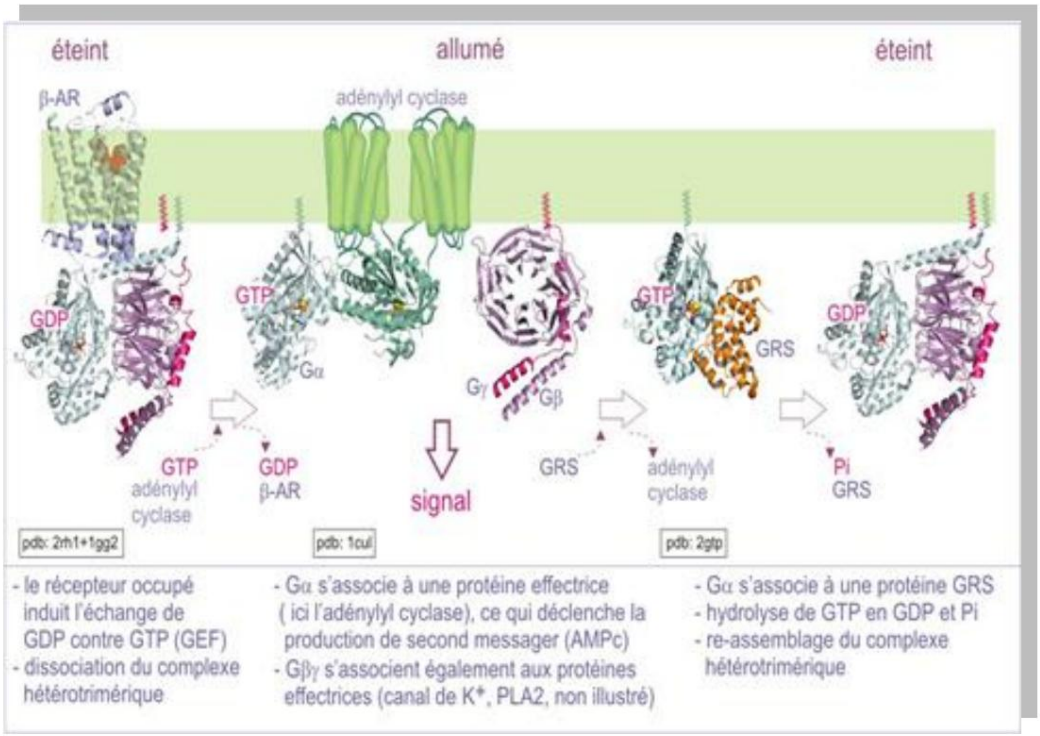


Figure 35: Role of the receptor, effector, and GRS protein in the GTPases cycle (Kramer and Tramu, 2013)

Interaction with the receptor activates the G protein (the alpha subunit releases GDP and (fixes GTP), which in turn will modulate the activity of an effector protein (which functions either with an enzyme or an ion channel) which produces the pharmacological effect

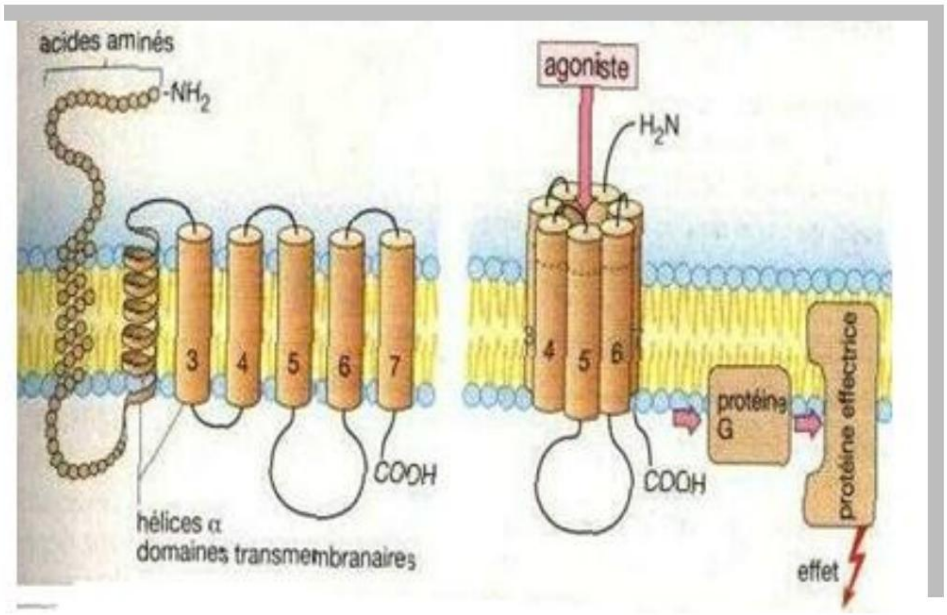


Figure 36: Binding of G protein with effector protein (Lüllmann et al, 2010)

This type of mechanism is common to the functioning of many receptors specific to certain endogenous molecules (Adrenaline - Dopamine - Histamine) or exogenous molecules (Morphins - All Opioids - Synthetic Hormones).

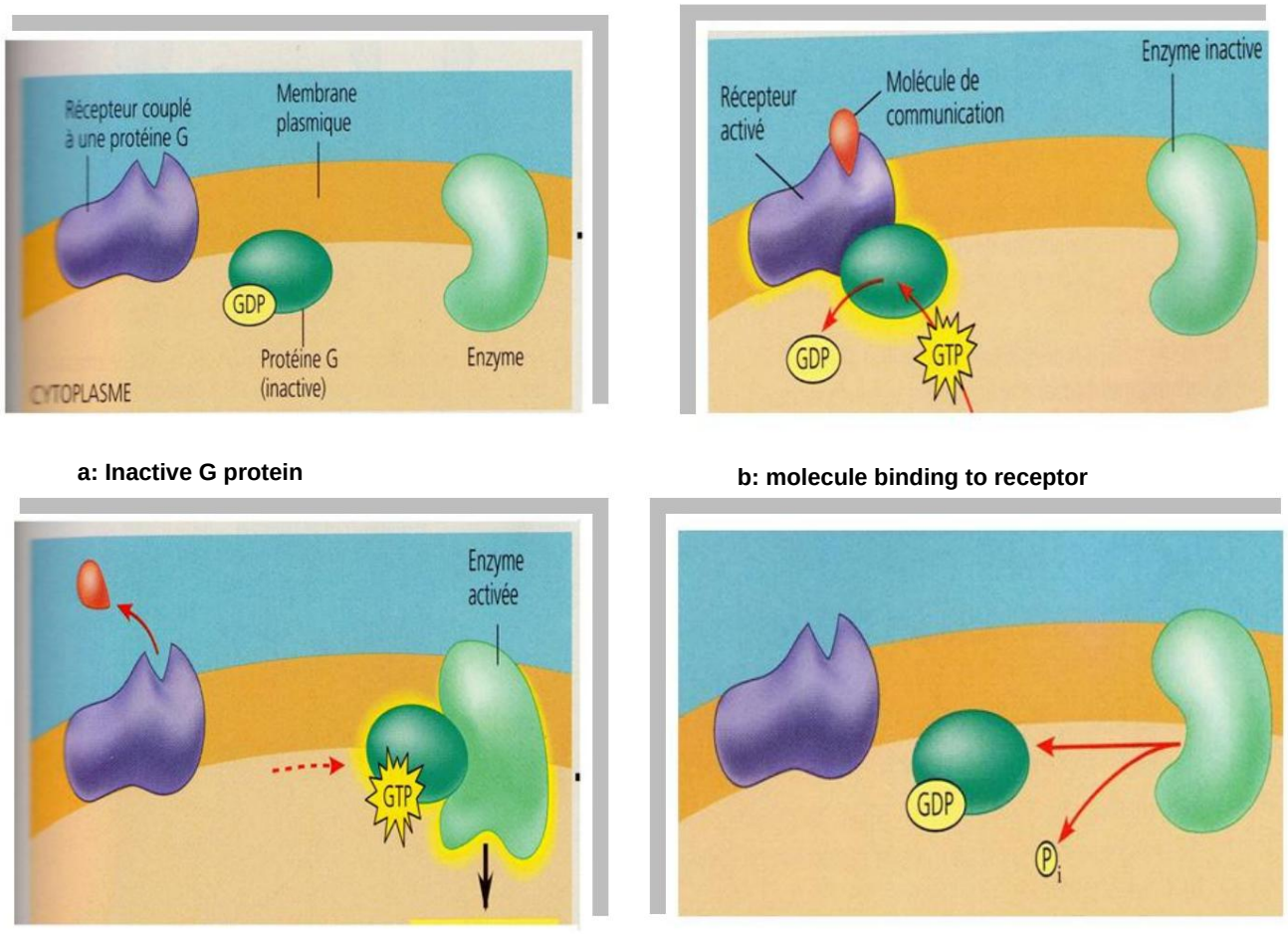
Among the effector proteins of G protein-coupled receptors, we must mention primarily adenylate cyclase (ATP - intracellular second messenger: inositol) triphosphate, diacylglycerol, cAMP), phospholipase C (phosphatidylinositol) and channel protein.

For example, an increase in cAMP concentration stimulates muscle tone smooth, the contractile force of the cardiac muscle and increases glycogenolysis and the lipolysis.

Inositol triphosphate (IP3) triggers the release of Ca+2 ions from stores intracellular, which triggers, for example, the contraction of muscle cells. smooth, and the breakdown of glycogen.

The alpha subunit of certain G proteins is capable of triggering the opening of a channel protein. This is how, for example, channels are activated potassium (action of opioids on the transmission of nerve excitation).

Example of (Guanosine triphosphate GTP)



a: Inactive G protein

b: molecule binding to receptor

c: activated enzyme

d: dephosphorylation

Figure 37: G protein-coupled receptor (Guanosine triphosphate) (Campbell and Reece, 2008)

IV.5.1.4.RECEPTORS, TRANSPORT PROTEIN

When the molecule crosses the membrane, it can form a "channel" or a Tunnel through which only one type of solution passes.

Example: Aquaporins (Specific protein tunnel). Or the protein of transport is a "permease" that oscillates between two conformations and moves a solute to through the membrane.

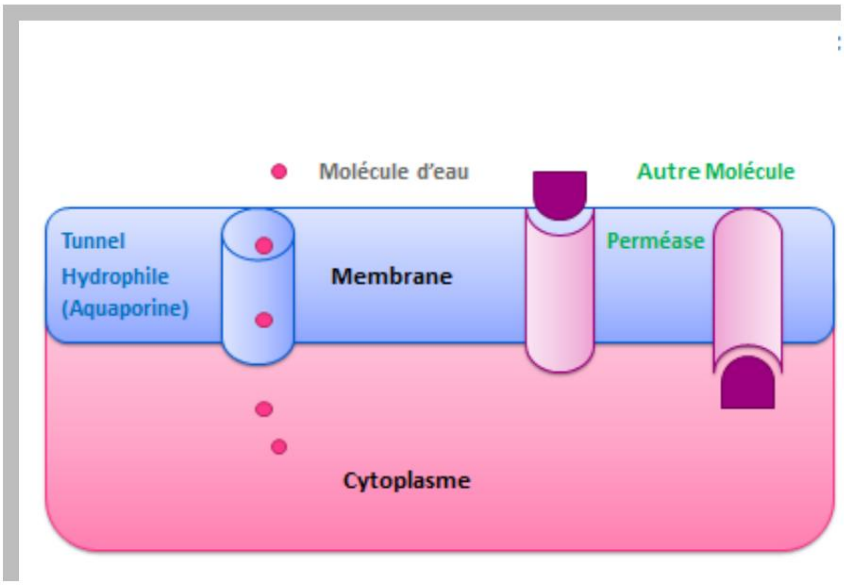


Figure 38: Aquaporins (specific protein tunnel) and permease

Example of drug carriers and their targets

Organic molecule transporters

- Norepinephrine/Serotonin — Antidepressants, cocaine, amphetamine
- Weak Acids — Probenecide

Ion transporters

- Na+/K+/2cl- cotransporter — Loop diuretics, furosemide
- Na+/K+ ATPase — digitalis cardiotonic glycosides
- Na+/H+ ATPase — Omeprazole

IV.5.1.5. In the cell nucleus

These are nuclear receptors, specific to many hormones such as thyroid and steroid hormones. They bind after being activated by the ligand on DNA and induce modifications in the transcription of certain factors, by for example, the stimulation of protein synthesis.

These hormones, which regulate gene expression in the nucleus, are lipophilic and diffuse freely across the cell membrane to reach the receptor.

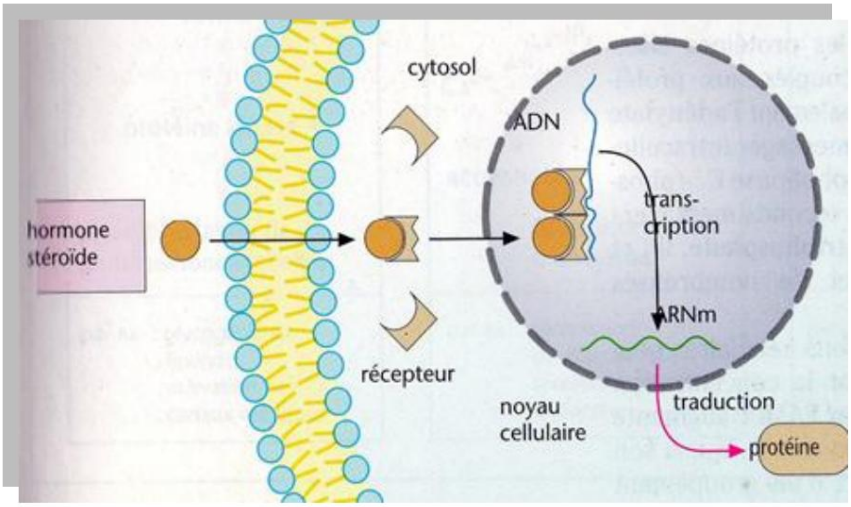


Figure 39: Nuclear receptor (Lüllmann et al, 2010)

Noticed:

- Some medications act through physicochemical interaction, as previously mentioned:
For example, the osmotic action of laxatives increases subliminal pressure and creates a call of water towards the intestinal lumen.

- Pathogens such as viruses, fungi, bacteria and parasites,
drugs act on specific targets of these agents such as enzymes,
receptors,
Examples:

Third-generation quinilone antibiotics such as enrofloxacin, which act by blocking bacterial DNA gyrase, and antiparasitic benzymidazoles, which act by blocking fumarate reductase, an enzyme necessary for parasite metabolism.

IV.6. CONCEPT OF AGONIST AND ANTAGONIST

IV.6.2. DEFINITION OF AGONIST

An **"Agonist** " or **"Mimetic",** is an exogenous molecule capable of binding to a receptor stimulates it and triggers a biological response.
An agonist mimics the effects of an endogenous ligand of the receptor (receptor activation).
Example: Ephedrine: an agonist of adrenergic receptors.

IV.6.1. DEFINITION OF ANTAGONIST

a **"Antagonist"** or **'Lytic"** is an exogenous molecule capable of binding to a receptor without producing biological response.

An antagonist acts by inhibiting the effects produced by an endogenous ligand (receptor inactivation). Ex: Phloroglucinol: muscarinic receptor antagonist.

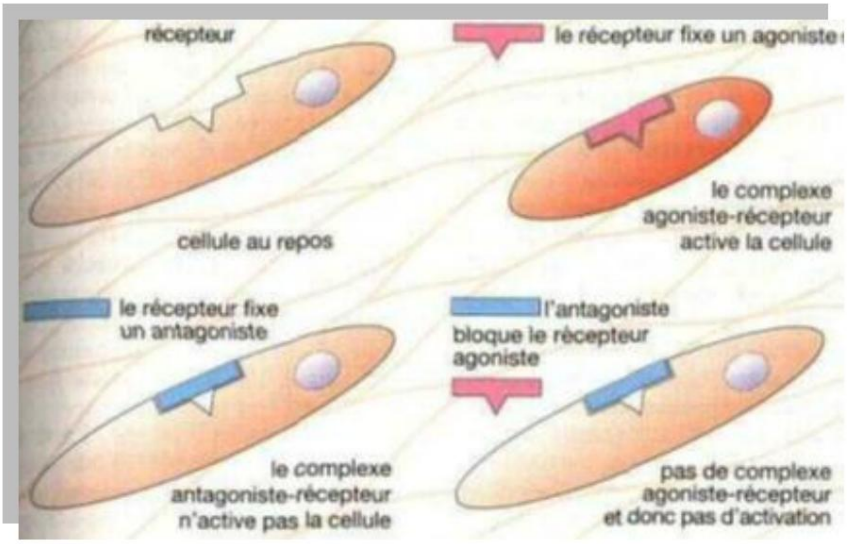


Figure 40: Agonist and antagonist (Lüllmann et al, 1998)

Two types of antagonists are described: **competitive antagonists and non-competitive antagonists**

ÿ **Competitive antagonists:**

When the antagonist binds to the receptor at the same site as the agonist, There is competition between the agonist and the antagonist with respect to the same site of action.

Direct antagonism

A competitive antagonist produces a reversible (surmountable) inhibition that can can be overcome by increasing the concentration of the agonist.

ÿ **Non-competitive antagonists:** The

antagonist binds to the receptor at a site distinct from the agonist's binding site (allosteric site). This is an indirect antagonism. It leads to conformational changes in the receptor, decreasing the receptor's affinity for its agonist.

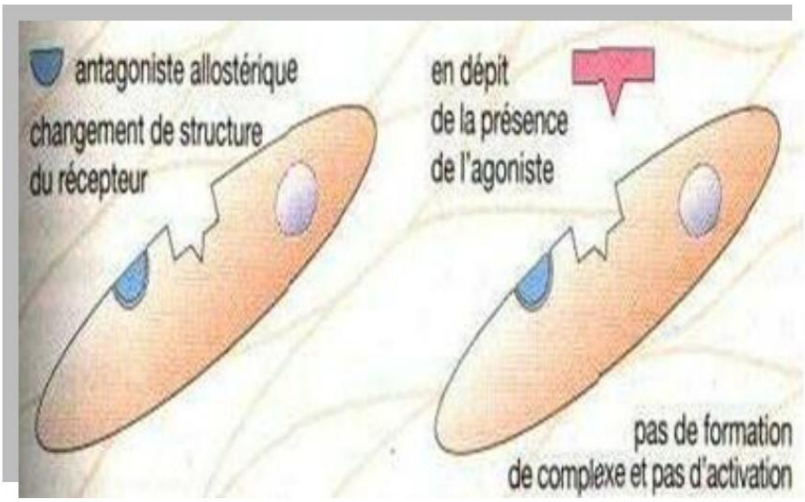


Figure 41: Indirect antagonism (Lüllmann et al, 1998)

A non-competitive antagonist elicits irreversible (insurmountable) inhibition.
which, in general, does not allow the agonist to produce a maximum effect.

Note: Antagonists have significant toxicological value.

IV.7. FUNCTIONAL EXPERIMENTAL APPROACH

IV.7. 1. DOSE-RESPONSE CURVE

By measuring the changes (i.e., the effects) made to a biological system by a substance at different concentrations, a curve can be established.

These curves are known in pharmacology as dose-response curves (or dose-action, dose - response).

The dose-response curve forms a sigmoid curve, which expresses the effect obtained (in (ordinates) according to the logo of the dose or concentration (on the x-axis).

The measured effect can be expressed as an absolute value or as a percentage of the effect. maximum.

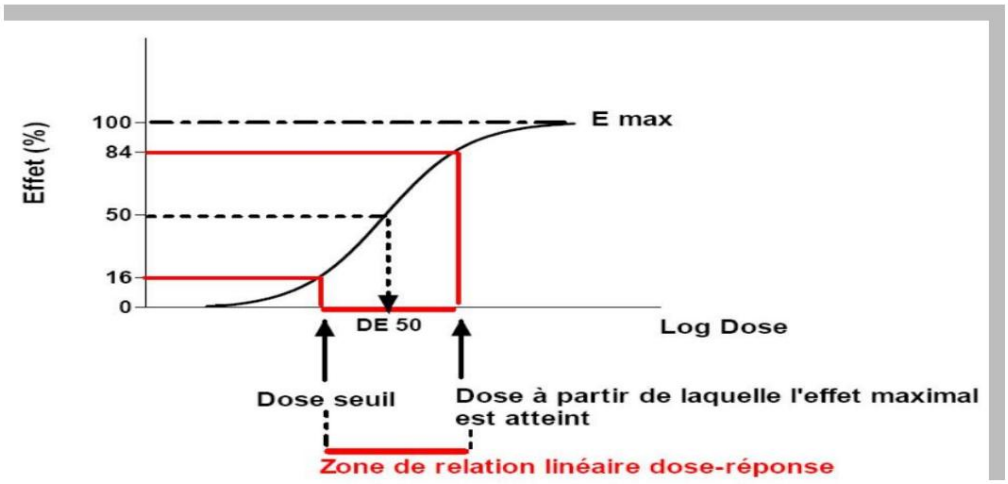


Figure 42: Dose-response curve (Combrisson, 2013)

The pharmacological effect is measured for increasing doses of the substance under study, either on in vivo models (in humans or animals) or on isolated organs (ex vivo models, for example, measurement of the contractile response on...)
isolated arteries).

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

IV.7.2. DISTINCTION BETWEEN THE CONCEPTS OF POWER AND EFFICIENCY

The dose-action curve of an agonist allows us to define: its efficacy and potency of the agonist.

ÿ **E max => measures the effectiveness of the agonist.**

ÿ **DE 50 or CE 50 => measures the power of the agonist.**

- Emax: maximum possible effect: this is the height of the plateau (curve 2).

- The ED50 (effective dose 50) (or power = EC50 effective concentration 50): dose of agonist which allows you to obtain 50% of its maximum effect (or half of the effect maximum 1/2 Emax).

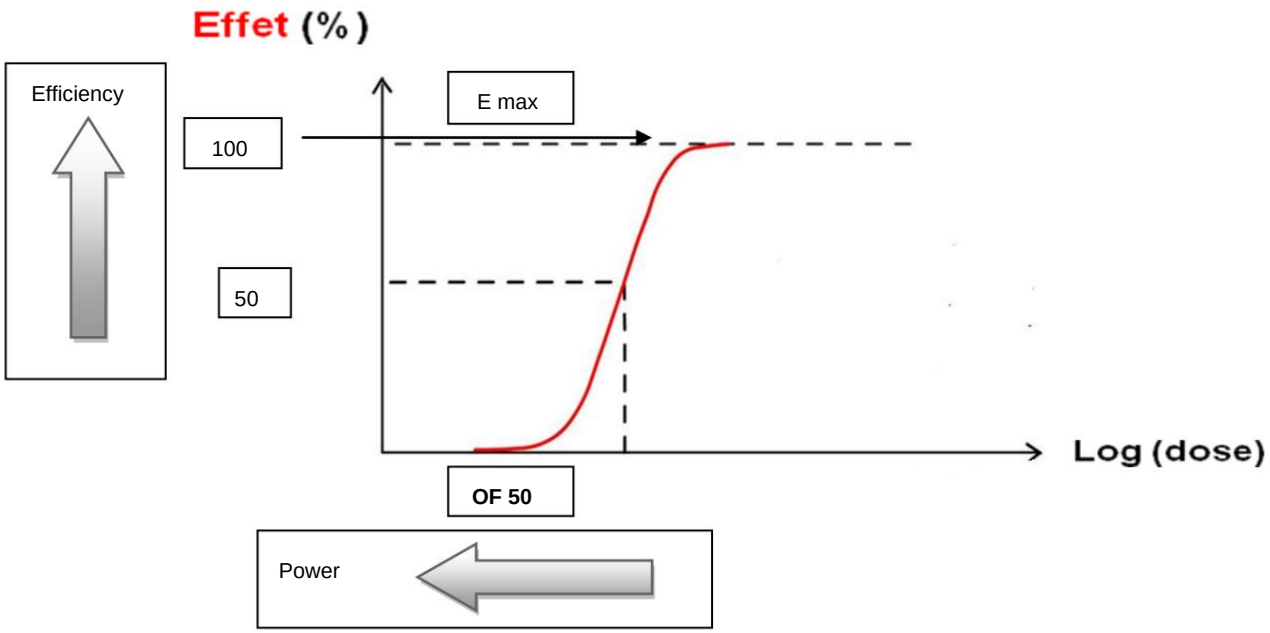


Figure 43: Efficacy and potency on the dose-response curve (Bousquet Melou, 2014)

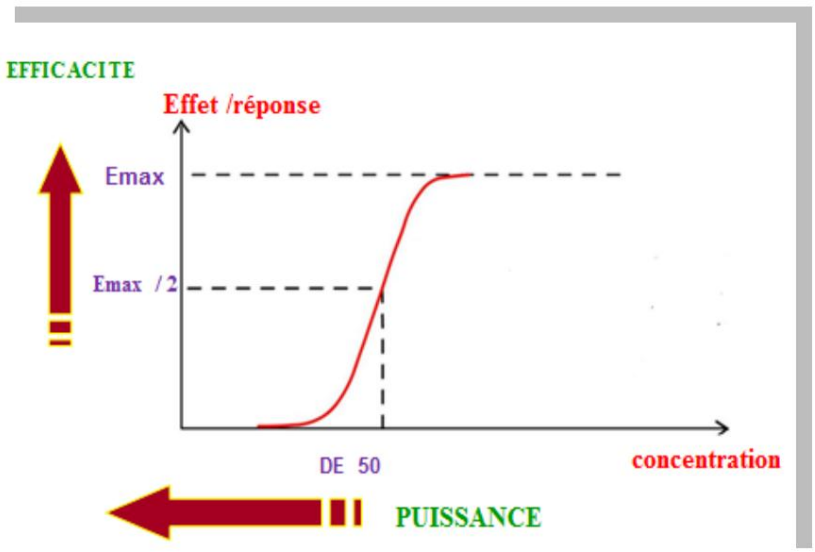


Figure 44: Distinction between the concepts of power and efficiency (Bousquet Melou, 2014)

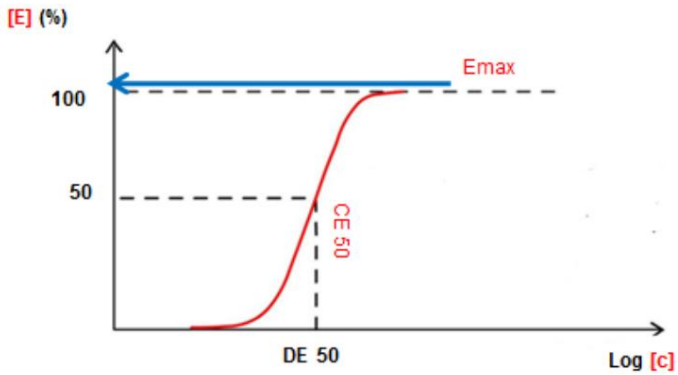
The ED50 is the parameter used to quantify the effect of an agonist. The ED50 characterizes the potency of the agonist.

The lower the DE50 of an agonist, the more powerful the agonist.

The dose-action curve of an agonist allows us to define its efficacy and potency.

The efficacy of a drug is its ability to generate a response when it binds to its receiver.

The maximum response obtained by a pharmacological effect varies from one agonist to another; the maximum response takes into account a factor ÿ, which expresses the activity intrinsic to each agonist.



Log [c] : dose
[E] : intensité de l'effet
E max : intensité maximale de l'effet
DE 50: dose efficace 50 ou puissance=CE50 concentration efficace 50

Figure 45: DE 50 on the dose-response curve

ÿ Emax => maximum possible effect: this is the height of the platform. The measurement of the effectiveness of the agonist

ÿ The ED50 (effective dose 50) (or power = EC50 effective concentration 50):
=>Dose of agonist that allows you to obtain 50% of its maximum effect (or half) of the maximum effect). The measurement of the agonist's potency

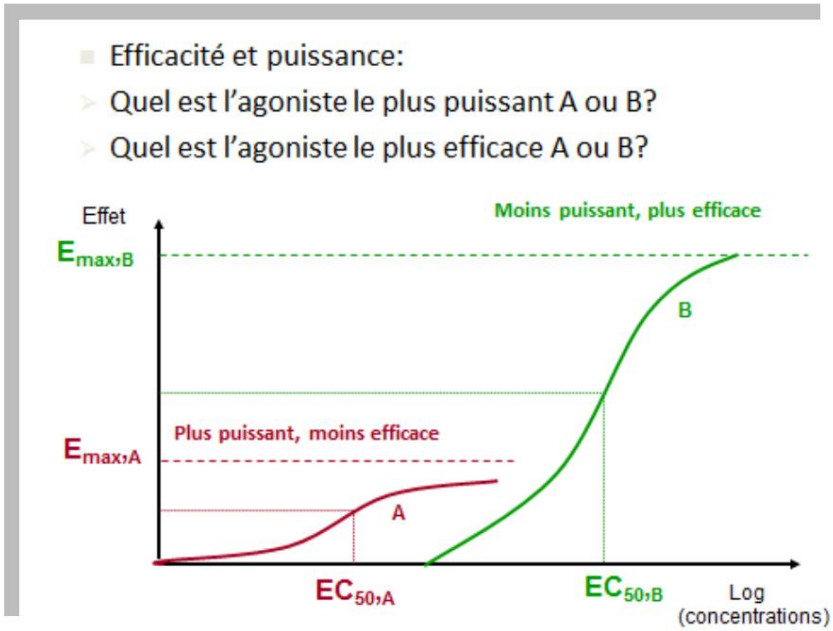


Figure 46: Efficacy and potency of two drugs (Bousquet Melou, 2014)

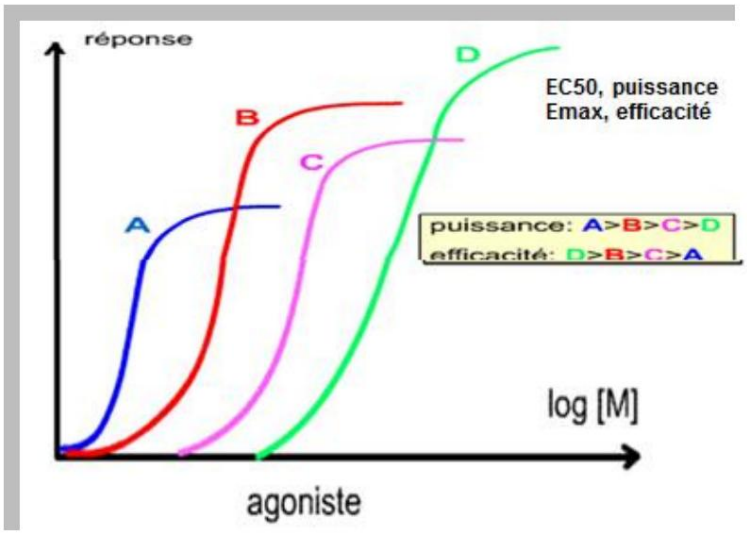


Figure 47: Potency and efficacy of several agonist ligands (Bousquet Melou, 2014)

Comparison of the dose-effect curves obtained for several agonists of a
The same receiver allows them to be classified by comparing their power and efficiency.
In the figure, A is more powerful than B and C.

The concept of power is based on that of affinity: the greater the affinity of an agonist
The larger the receiver, the higher its power.

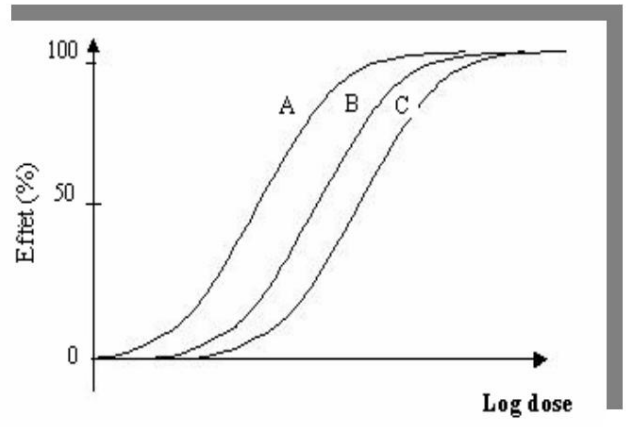


Figure 48: Integer agonists (ABC)

A, B, and C are capable of producing the maximum effect; they have the same efficiency, and this are **full agonists.**

IV.7.3. CONCEPT OF AFFINITY CONSTANT

Agonist concentration required to occupy 50% of receptors = constant characterizing the drug's affinity for its receptor; the lower the Kd, the higher the affinity.
is high.

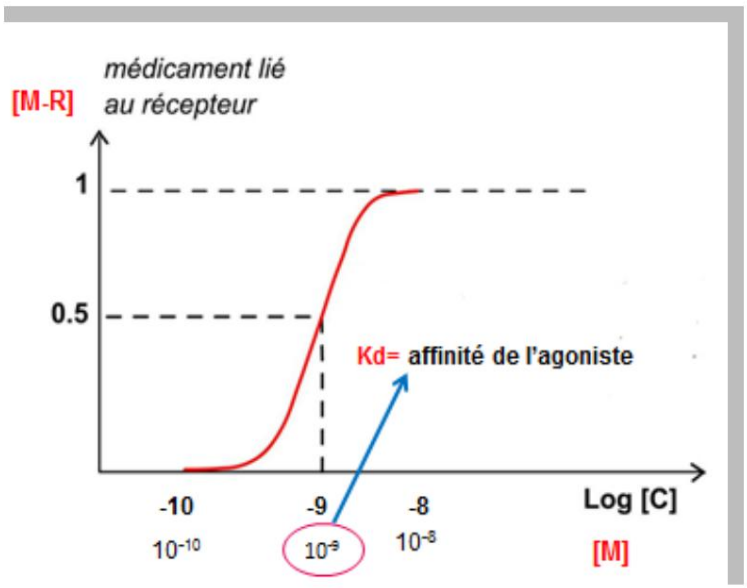


Figure 49: Affinity constant (Bousquet Melou, 2014)

IV.7.4. AGONIST

• A drug that produces an effect similar to that of the natural mediator (endogenous ligand) after binding to its target.

• The maximum pharmacological effect obtained varies from one agonist to another.

• **Whole** or pure agonist: produces the maximum effect.

• **Partial agonist** (incomplete response): effect < maximum effect,

• Its affinity for the receptor is lower than that of the pure agonist

Efficiency: A > B > C

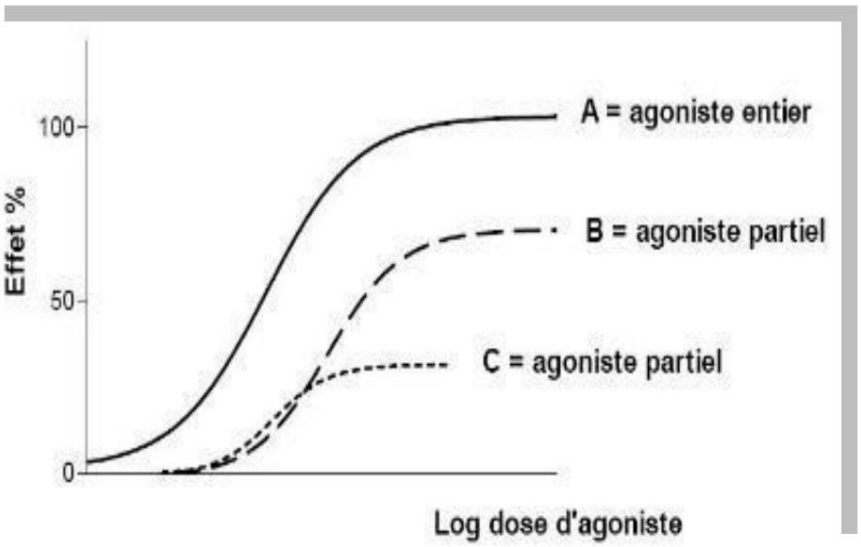


Figure 50: Full and partial agonist

The maximum response obtained by a pharmacological effect varies from one agonist to another. another; the maximum response takes into account a **factor ÿ** specific to each agonist, it is the intrinsic activity of the agonist (efficacy).

Intrinsic activity allows us to define agonists, which varies from 0 to 1.

– If ÿ=1 integer agonist,

– If 0<ÿ<1, partial agonist

A complete or pure agonist **(ÿ=1):** can produce a maximal response in occupying all or a fraction of the receptors,

A partial agonist **(0<ÿ<1):** cannot produce a maximum response recorded by full agonists (maximum response less than AE) even when it occupies all the receptors.

IV.7.5. ANTAGONIST

A substance that binds to a specific receptor without causing any effect (no cellular response), and that blocks the action of the endogenous mediator (prevents its binding to the receiver).

There are two types of antagonists :

– Competitive antagonist: binds at the same site as the endogenous mediator (competition for the connection on the same site)

– Non-competitive antagonist: binds to another site on the receptor

Since the antagonist has no effect of its own, it lacks intrinsic activity; that is to say... that is to say: the ability to induce a response following its binding to a receptor.

IV.7.6. AGONIST-ANTAGONIST

With a dual potential as both agonist and antagonist.

• In the absence of the endogenous mediator (or in very low quantity) it is a partial agonist.

• In the presence of the endogenous mediator or an entire agonist is an antagonist.

Example : Buprenorphine (TEMGESIC) ÿ Nalbuphine

• Decreased effectiveness of morphine

- Binding to µ opioid receptors: analgesic effect.
- In the presence of morphine: displaces morphine from the receptors (effect antagonist).
- A partial agonist has a dual potential as both agonist and antagonist.

• When the endogenous mediator is absent or present in very low quantities at the receptor, the partial agonist will bind to the receptor and exert its agonist effect partial.

• When the endogenous mediator (which has the quality of a full agonist) is in higher concentration or when a full agonist is also present, the substance in question will compete with the endogenous mediator or the full agonist.

• If the substance in question has sufficient affinity to displace the endogenous mediator or the entire agonist, the partial agonist will act as an antagonist.

• When the endogenous mediator (which has the quality of a full agonist) is in higher concentration or when a full agonist is also present, the substance in question will compete with the endogenous mediator or the full agonist.

• If the substance in question has sufficient affinity to displace the endogenous mediator or the entire agonist, the partial agonist will act as **an antagonist.**

• For example, pentazocine (Fortal®), a partial agonist of ÿ-opioid receptors, is When used alone, the morphine analgesic acts as an agonist of ÿ-opioid receptors. However, in the presence of morphine, for example in morphine addicts, it acts as an antagonist: it displaces morphine from the ÿ-opioid receptors.

It induces symptoms similar to morphine withdrawal syndrome.

• Ex: the use of opioid analgesics leads to the disappearance of pain but also unpleasant side effects such as euphoria, for example,

• Euphoria is a feeling of well-being observed primarily in humans, which falls asleep when taking morphine (less anxiety, less distress).

• Thus, the phenomenon of psychological and physical dependence develops in humans, which is explained by the desire to reach this state again by repeating the administration of opioids with increasingly higher doses.

IV.8. ADVERSE EFFECTS

• Any harmful and unintended reaction of a medicine when used as directed under the terms of its marketing authorization (MA) or during any other use (overdose, misuse, drug abuse, medication error).

• Two main types

– Predictable side effects: related to pharmacological properties (dose-related) (more often)

– Unpredictable side effects: unrelated to pharmacological properties

• Very frequent (>=1/10). -Frequent (>=1/100 to <1/10).

• Uncommon (>=1/1000 to <1/100).

• Rare (>=1/10,000 to <1/1,000). -Very rare (<1/10,000)

Medications are intended to have only therapeutic effects, but often undesirable side effects are associated with this activity. The severity of these side effects varies, and they must be minimized by...

pharmacologists report mild effects (e.g., nausea), sometimes, side effects which the symptoms that appear are quite serious (e.g., aplastic anemia).

These side effects assess the toxicity of the drug, which is expressed by the measurement of the LD50 (Lethal Dose 50).

The LD50 assesses the dose of a drug capable of killing 50% of a group of experimental animals; this LD50 is defined in each experiment for development.
of a new drug.

The higher the LD50 of a drug, the less toxic the drug and the fewer the effects.
minor side effects.

IV.9. SELECTIVITY/SECURITY

Therapeutic index: ratios between therapeutic concentrations or toxic

• Example: Antihistamines (Antagonists)

They block histamine receptors

• H1 receptors: Bronchi, Skin, Capillaries. Activation of these receptors leads to muscle contraction, increased heart rate, increased...
Increased vascular permeability, therefore redness and itching

• H2 receptors: Stomach. Are responsible for an overproduction of gastric acid.

• H3 receptors: Neural tissue

These receptors determine a negative regulation, a natural brake on production of histamine (the wakefulness hormone). The main side effect of these sites is based on these sites.

Antihistamines → Drowsiness

IV.10. SELECTIVE MEDICATION

For a drug to have therapeutic value, its action must be targeted and limited to a specific biological mechanism: this is called a specific effect.

Often a molecule does not have absolute specificity for a biological mechanism: its activity may extend to different receptors but with varying affinities. high for a given receptor than for others. We will speak of a selective molecule for a given receptor. This is called binding selectivity or effect selectivity.

ÿ **TOLERANCE**

The decrease in the pharmacological effect of a dose of medication during repeated administration of the same dose.

To regain the effect of the initial dose, it is necessary to increase the dose. administered.

ÿ **PHARMACODEPENDENCE**

Repeated, compulsive use of a drug for the chemical pleasure it provides or to avoid the unpleasant effects of its suppression (withdrawal syndrome).

Physical dependence with withdrawal syndrome

Compulsive psychological dependence

Examples: Opioid analgesics, barbiturates, benzodiazepines

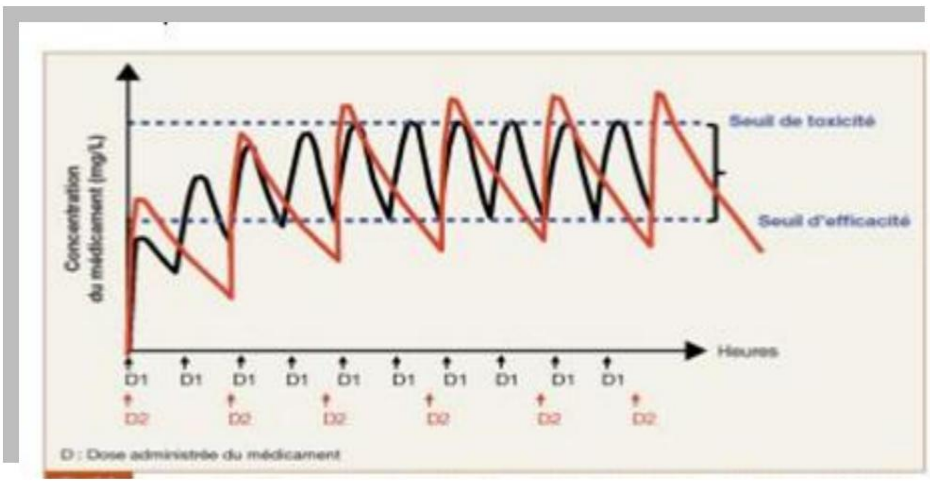


Figure 51: Dose-effect curve in the case of non-compliance with the dosage

The dosage and the interval between doses must be strictly adhered to in order to avoid:

1- To expose the patient to a toxic risk. 2-Periods of inefficiency.

IV.11. DRUG INTERACTIONS

There are two types of interactions:

Pharmacokinetics very common: Disruption of the fate of certain drugs.

Pharmacodynamics: Mechanisms of action at the receptor level.

• Changes in pharmacodynamic and/or pharmacokinetic effects of a drug resulting from the concomitant intake of another drug, of a food or the consumption of alcohol or tobacco

• Must be **clinically significant**

• **Beneficial** •

Unfavorable+++ÿ toxicity and/or ineffectiveness

IV.11.1. ABSORPTION

- A decrease in the amount absorbed may result in a concentration lower than the concentration therapeutic.

- Decrease in Absorption Rate: modification of Cmax and Tmax.

Interaction factors:

- Gastrointestinal motility: Delayed gastric emptying.
- Food bolus: decreased absorption.
- Formation of complexes ÿ decreased absorption.

Example : Fluoroquinolones calcium salts ÿ takenand separate .

Action on pH:

Changes in stomach acidity can alter the absorption of other medications.

Example : Antacids are medications absorbed in acidic form and ÿ need to shift medication intake; **creation** ·

of a physical barrier

Example: SMECTA® (Diosmectite) ÿ administration of the other drug at a distance from SMECTA® .

Clinical interest

– Activated charcoal captures medications in the digestive tract and prevents their absorption absorption

ÿ Use in suicide attempts.

IV.11.2. DISTRIBUTION

– Binding to plasma proteins.

– The drug with the highest affinity binds first and increases the free form active of the second.

IV.11.3.LEPATIC METABOLISM

- When 2 drugs are metabolized by the same enzyme system

ÿ Competition ÿ risk.

- Enzyme inhibitors.

– Decreased metabolism of other drugs.

Accumulation leads to overdose.

- Enzyme inducers.
  - Increased metabolism of other drugs.

ÿ Decreased efficiency.

- Action of inhibitors and inducers primarily on cytochromes P450 (CYP450) in the liver.

- When 2 drugs are metabolized by the same enzyme system

ÿ Competition ÿ risk.

- Enzyme inhibitors.
  - Decreased metabolism of other drugs.

Accumulation ÿ overdose

- Enzyme inducers.
  - Increased metabolism of other drugs.

ÿ Decreased efficiency

- Action of inhibitors and inducers primarily on cytochromes P450 (CYP450) in the liver.

IV.11.4. DRUG COMBINATION

- **Additivity:** Effect of (A+B) = Effect of A + Effect of B.
- **Synergy or Potentiation:** Effect (A+B) > Effect of A + Effect of B.

=> ÿ Therapeutic effect, desired combinations, beneficial. =>ÿ

Benefit/risk ratio.

=>ÿ Drug dosages.

• **Antagonism:** Effect of (A+B) < Effect of A + Effect of B.

=> Therapy failure, increased risk of adverse effects.

Included in the **SPC** (Summary of Product Characteristics).

• **Contraindication**

– It has an absolute character and must not be transgressed.

• **Association not recommended**

– To be avoided, study the benefit/risk ratio, and closely monitor the patient. •

Use with caution+++

– Association possible if recommendations are followed (clinical monitoring) and biolog.).

– Ex: tetracyclines + calcium => ÿ decreased digestive absorption of tetracyclines: taken at distance from the cyclines (2h).

• **To be taken into account**

– Additive adverse effects+++ ; no practical recommendations can be made. The physician assesses the appropriateness of the combination.

– Ex: zopiclone + erythromycin => slight increase in sedation. • **Example 1:**

Drug Interactions

- Infusion incompatibilities.

– Physico-chemical incompatibilities.

– Precipitation of 2 mixed drugs.

=>Respect for dilution solutions because of the risk of vascular embolism.

• **Example 2:**

– Vancomycin + Sodium Heparin.

– Amphotericin B + NaCl.

Course of action

• Always check the compatibility of injectable medications.

• Flush the IV line before injecting a second product.

IV.12. VARIABILITY OF PHARMACOLOGICAL RESPONSE

The pharmacological effects of a drug can vary from one individual to another.
or even in the same individual regardless of dose or pharmacokinetics.

This pharmacodynamic variability concerns both beneficial and adverse effects. It manifests as an unusual response to the drug. A patient may be observed to be "hypo-reactive" or "hyper-reactive" depending on whether
the intensity of the response to a given dose is weaker or greater than that
observed in the majority of individuals. One can observe a **"Hypo-reactive"** patient or
on the contrary " **Hyper-reactive"** compared to the majority of individuals.

Typical example in the ISV Constantine canine clinic:

Acepromazine (INN).

Calmivet (ND).

Vetranquil (ND).

Manufacturer's suggested basic dosage: 0.25ml/10kg body weight, for small animals
species.

Clinical observation:

- Poodle dog weighing 4 to 5 kg does not respond to the 2 ml dose.
- Cat (in some cases), approximately 3 kg does not respond to a total dose of 1.5 ml.
- German Shepherd dog, 30 to 35 kg, completely calm after 10 minutes
  with a total dose of 1ml.

IV.13.FACTORS INFLUENCING PHARMACOLOGICAL EFFECT

This variability may be related to:

- Physiological state: age, gestation, lactation.
- Pathological condition: renal failure, hepatic failure, pathology
  old.
- Drug interactions.
- Individual sensitivity of genetic or non-genetic origin.
- To the specific effects of the drug, such as tolerance and dependence.

Tolerance corresponds to the decrease in the pharmacological effect of a dose of drug when the same dose is administered repeatedly.

To regain the effect of the initial dose, it is necessary to increase the dose. administered.

Drug dependence, according to the World Health Organization, is defined as: "the repeated, compulsive use of a drug or non-drug product"
for the chemical pleasure it provides or to avoid the unpleasant effects of its "Deletion."

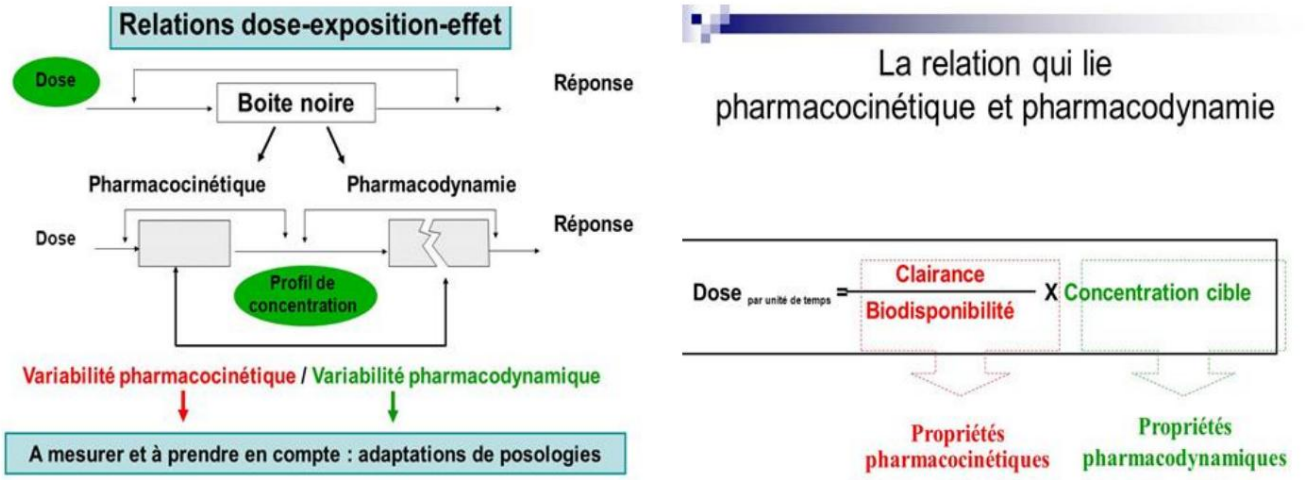


Figure 52: Pharmacokinetic and pharmacodynamic link (Bousquet Melou, 2014)

CONCLUSION GENERAL

GENERAL CONCLUSION

The study of the kinetics of a xenobiotic makes it possible to know its fate in the organism based on data relating to the physico-chemical properties of the substance on the one hand and the anatomo-physiological characteristics of the animal species on the other. considered on the other hand. Its therapeutic and toxicological consequences are obvious.

Knowledge of pharmacodynamics is necessary to rationalize the Prescribing medication. It therefore allows for greater effectiveness and tolerance of these drugs. It also provides reliable bases for the creation of new therapeutic molecules. Depending on the physiological specificity of the animal species considered, dosage adjustment is represented by the quantification of active ingredient per unit of time. Thus, this dose depends on the pharmacokinetic properties of the molecule on the one hand and on its pharmacodynamic properties on the other. These factors of variability act on the concentration profile and of the dose-response relationship.

All these investigations should ensure animal welfare and safeguard also the environment as well as humans consuming healthy animal products.

In the end, this handout proved very stimulating due to the desire to prepare a future document to address the various practical exercises carried out by the team, and Why not another one dedicated to specialized pharmacology? Our ambition remains to to do one's best.

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IMPORTANT

La traduction est assurée par Google traduction mais qui na pas encore

été corrigée. La version finale est cours…

KEEP IN MIND

The translation was performed by Google Translate, but it hasn't been corrected yet

We are currently working

on the final version.