

PHARMACOKINETICS  
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LECTURE 1: INTRODUCTION, CONCEPTS, & THE USES OF PHARMACOKINETICS



# General

- **Biopharmaceutics** is a major branch in pharmaceutical sciences which relates between the physicochemical properties of a drug in dosage form and the pharmacology, toxicology, or clinical response observed after its administration.
- **Pharmacology** is a branch of medicine and pharmaceutical sciences which is concerned with the study of drug or medication action, where a drug can be broadly or narrowly defined as any man-made, natural, or endogenous molecule which exerts a biochemical or physiological effect on the cell, tissue, organ, or organism.
- **Toxicology** is the scientific study of *→ adverse effect* adverse effects that occur in living organisms due to chemicals. It involves observing and reporting symptoms, mechanisms, detection and treatments of toxic substances, in particular relation to the poisoning of humans

# General definitions

- **Toxicokinetics** which is the study of kinetics of absorption, distribution, metabolism, and excretion of a **xenobiotic** under the conditions of toxicity evaluation (is pharmacokinetics studied at high doses (toxic?).  
لعادة عزيمتها كالمعتاد الجسم زي الدواء
- **Clinical Pharmacokinetics** is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient.
  - **Traditional pharmacokinetic** studies collect several blood samples from **healthy volunteers** at **fixed, planned times**. In contrast, **population pharmacokinetic** studies use samples from **patients receiving routine treatment**, who often get **different doses** and have their blood taken at **irregular, clinically driven times**.

# What is pharmacokinetics?

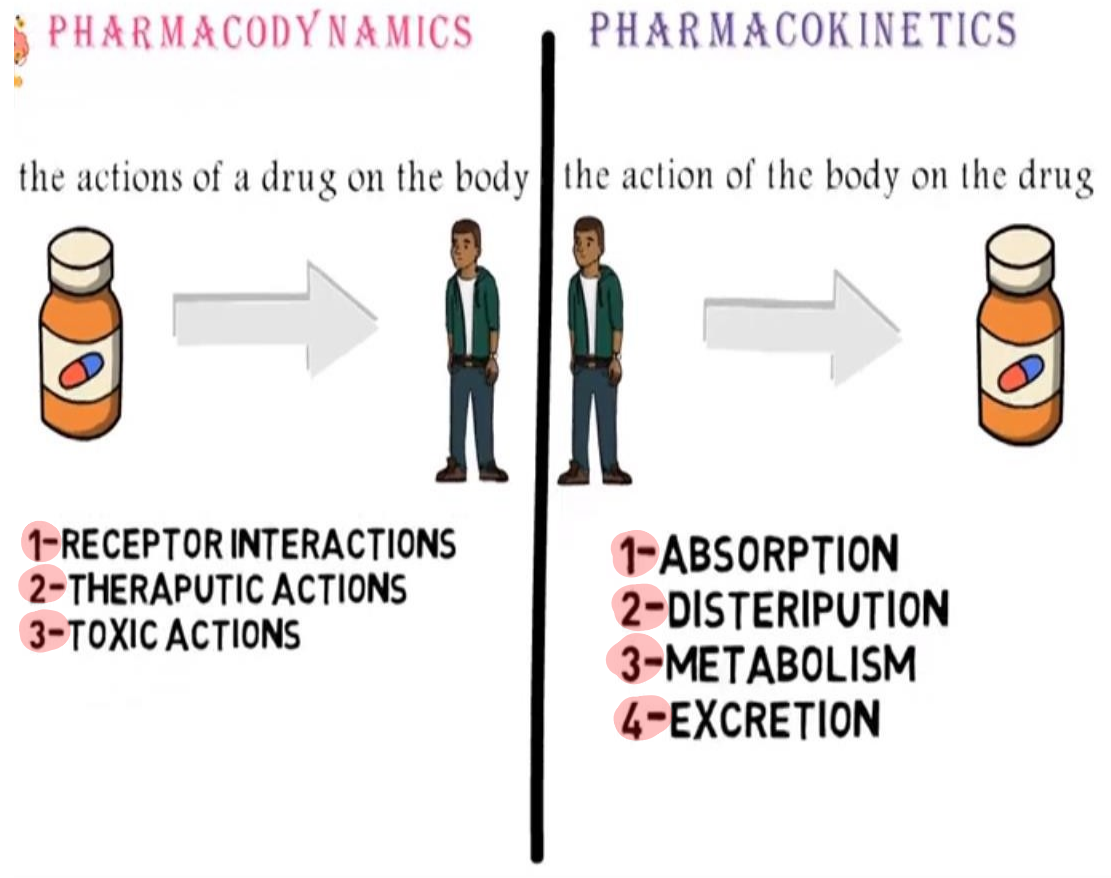
- **Pharmacokinetics** describes the movement (Greek– kinesis) of a drug (Greek – pharmakon) around the body.  
*drugs*
- **Pharmacokinetics is the branch of pharmacology** dedicated to determining the fate of chemical substances administered to a living organism – ‘what the body does to the drug’.  
*↳ ADME  
or AD + Elimination*

# Pharmacodynamics

- **(pd) Pharmacodynamics** is the science that studies the relationship between the drug concentration at the site of action (receptor) and its pharmacological response.

- Drug + receptor → Pharmacological response or toxic response.

*what the drug does to the body?!*



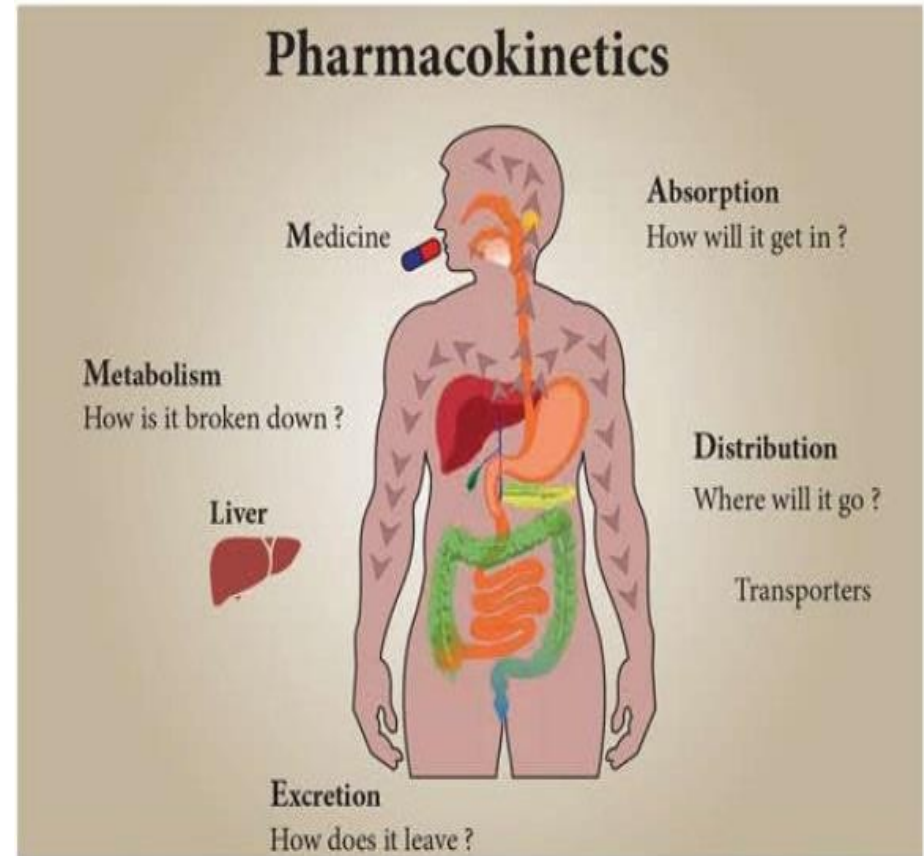
# PHARMACOKINETICS (PK) Principles

- **The science of the kinetics (the study of the rates) of drug absorption, distribution, metabolism and excretion of a drug and its metabolite(s).**
- **Drug distribution and elimination = Drug disposition.**

↳ متى الدواء يتصرف داخل الجسم

↳ Metabolism, excretion

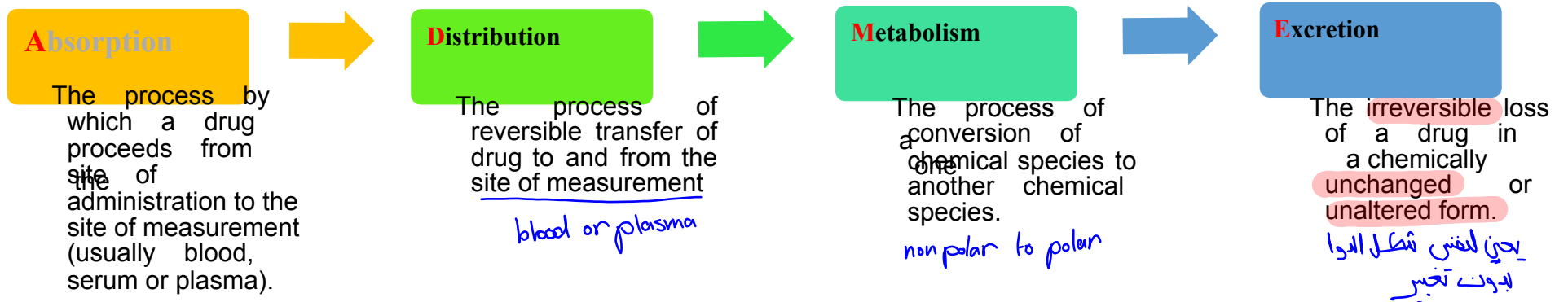
pharmacokinetic is Absorption + disposition or  
absorption + distribution + elimination or ADME



# Review of **ADME** Processes

- **ADME** is an acronym representing the pharmacokinetic processes of:
- **A** : Absorption  $\Rightarrow$  barrier present  $\begin{cases} \text{IV just disposition (barrier not present).} \\ \text{orally disposition and absorption} \end{cases}$
- **D** : Distribution reversible process / From blood to tissue and reverse
- **M** : Metabolism drug  $\begin{cases} \text{non-polar to polar} \\ \text{lipophilic to hydrophilic} \end{cases}$
- **E** : Excretion.

# ADME process



# ADME

- Elimination: the irreversible loss of drug from the site of measurement. (blood or plasma)  
excretion إخراج الدواء من الدم
- **Metabolism and excretion processes represent the elimination process.**
- **Elimination = Metabolism and Excretion.**

## Pharmacokinetics tries to answer the questions:

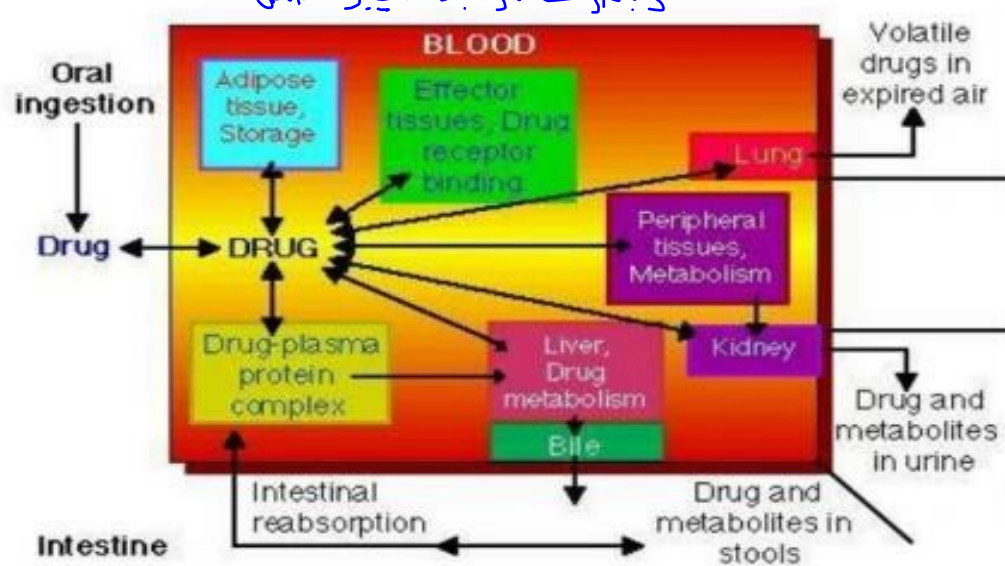
- Why does only a fraction of the total dose reach its target?
- How should we dose (route) and how many times (frequency) to maintain drug at target (efficacy)?

because of the first pass metabolism and incomplete absorption and protein binding

طريقة الإعطاء  
 نختار الحقن الوريدي اذا اردنا وصول الدواء كاملا وبسرعة  
 نختار الفم للراحة في الحالات المزمنة، مع زيادة الجرعة لتعويض المفقود في الكبد تكرار الجرعة  
 يعتمد بشكل اساسي على عمر النصف وهو الوقت الذي يحتاجه الجسم للتخلص من نصف كمية الدواء اذا كان الدواء يخرج بسرعة من الكلى او الكبد نحتاج لاعطائه عدة مرات في اليوم الهدف هو الوصول الى حالة الثبات حيث تكون كمية الدواء الداخلة للجسم مساوية للكمية الخارجة منه

## DRUG DISPOSITION

لماذا يتصرف الدواء بعد ما يغير اختصاصه



# WHY DO WE NEED PK?

1. Determining the "Right Dose"
2. Setting the (Frequency)
3. Choosing the Best "Route" (Bioavailability)
4. Individualized Medicine (Patient Factors)

Not everyone processes drugs the same way. PK is essential for adjusting doses for specific people:  
 Kidney/Liver Disease: If a patient's "filters" aren't working, PK helps calculate a lower dose so the drug doesn't build up to dangerous levels.  
 Age: Infants and the elderly have different metabolism rates; PK provides the math to keep them safe.

# How Do We Do PK?

## PERFORMING A PK STUDY

DOSE

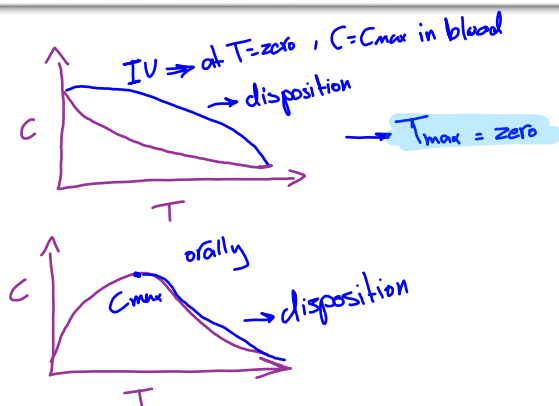


COLLECT SAMPLES (BLOOD, URINE, BILE, FECES)  
AT VARIOUS TIMEPOINTS

ANALYZE FOR  
DRUG/METABOLITES

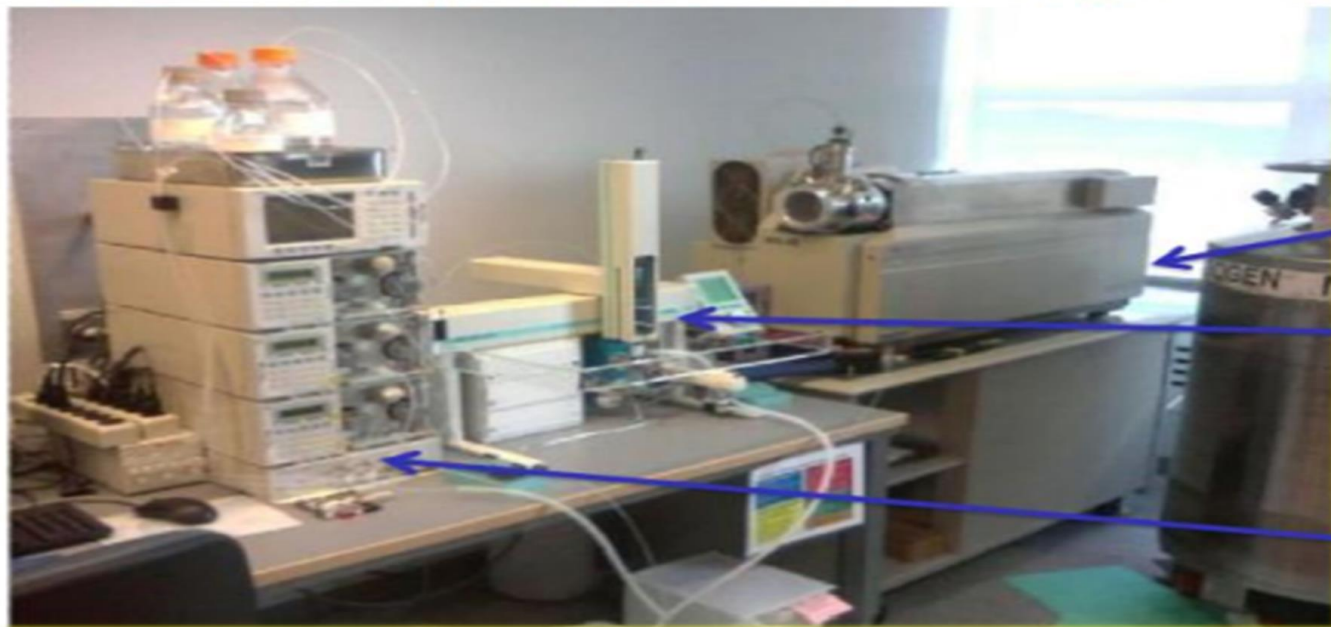


PK DATA ANALYSIS



# How is the Data Generated?

## Plasma Concentration vs Time Curves

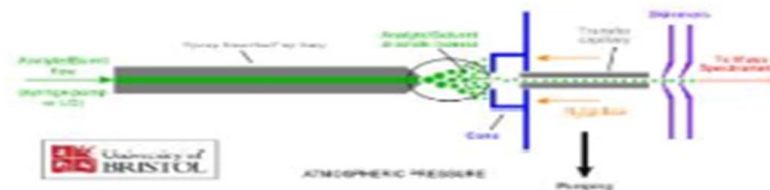


mass spectrometer

HTS autosampler

HPLC

Electrospray ionization MS revolutionized drug discovery! (plasma, urine, bile analysis)



# Concept & Uses of Pharmacokinetics

- In practice, pharmacokinetics usually focuses on **concentrations of drug in blood plasma**.
- Formal interpretation of pharmacokinetic data consists of fitting concentration-versus-time data to a model and determining parameters that describe the observed behaviour.
- **Plasma concentrations (C<sub>p</sub>)** are therefore useful in the early stages of drug development, and in the case of a few drugs plasma drug concentrations are also used in routine clinical practice to: why?!
- **Individualize dosage**, to achieve the desired therapeutic effect while minimizing adverse effects in each individual patient – an approach known as **therapeutic drug monitoring**, often abbreviated **TDM**.

تخصيص جرعة لكل فرد

بعض الادوية تكون خطيرة او دقيقة جدا بمعنى ان الفرق بين الجرعة التي تشفى والجرعة التي تسمم هو خيط رفيع جدا  
It is called narrow therapeutic effect  
الوظيفة: بدلا من اعطاء نفس الجرعة لكل الناس نقوم بقياس تركيز الدواء في دم المريض فعليا ثم نعدل الجرعة لتناسب جسمه هو فقط

# Therapeutic Drug Monitoring (TDM)

- Table 1.1 shows examples of some drugs where a therapeutic range of plasma concentrations has been established, enabling TDM. Concentrations of drug in other body fluids (e.g. urine, saliva, cerebrospinal fluid, milk) may add useful information.

**Table 1.1: Examples of drugs where therapeutic drug monitoring (TDM) of plasma concentrations is used clinically**

Category	Example(s)
Immunosuppressants	Ciclosporin, tacrolimus
Cardiovascular	Digoxin
Respiratory	Theophylline
CNS	Lithium, phenytoin
Antibacterials	Aminoglycosides
Anticancer drugs	Methotrexate

*narrow therapeutic index*  
*ضيق*

# Concept & Uses of Pharmacokinetics

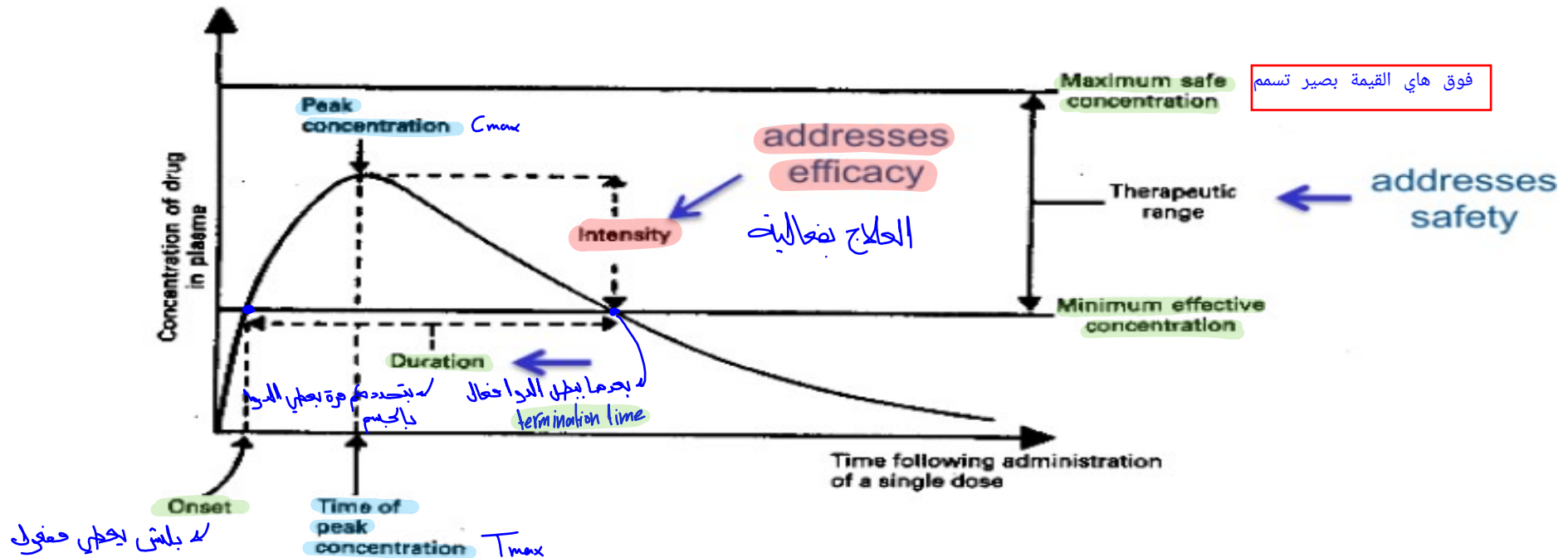
- Some descriptive pharmacokinetic characteristics can be estimated directly by inspecting the time course of drug concentration in plasma following dosing – **important examples**, are the maximum plasma concentration following a given dose of a drug administered in a defined dosing form ( $C_{max}$ ) and the time ( $T_{max}$ ) between drug administration and achieving  $C_{max}$ .

لما تكون الجرعة عالية جدًا قد يسبب الدواء التسمم  
وإذا كانت منخفضة جدًا قد لا يفي التأثير العلاجي

إذا كانت  $T_{max}$  قليلة يعني الامتصاص سريع  
أيضا لو كانت عالية فهذا يعني أن الامتصاص بطيء

# Descriptive Pharmacokinetic Characteristics

## Plasma Concentration vs Time Curves



Relationship between the plasma concentration–time curve obtained following a single extravascular dose of a drug and parameters associated with the therapeutic or pharmacological response

# Applications of Pharmacokinetics

- Bioavailability measurements. تحديد كمية الدواء التي تصل فعلياً الى الدورة الدموية وسرعة وصولها كمية الدواء التي ينتجها الكبد من نفس المادة التي يتوصل لها
- Effects of physiological and pathological conditions on drug disposition and absorption. فسيولوجية: مثل كبار السن الذين يقل لديهم تدفق الدم للكلى.  
مرضية: مثل مريض التليف الكبدي الذي لا يستطيع تكسير الدواء بكفاءة.
- Dosage adjustment of drugs in disease states, if and when necessary. في حالة مشاكل الكبد بنقل جرعة الادوية لهذا المريض
- Evaluation of drug interactions. بعض الادوية تمنع الانزيمات التي تكسر ادوية اخرى مما يؤدي لارتفاع مفاجئ وخطير في تركيز الدواء الثاني في الدم
- Clinical prediction: using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy. السريري التنبؤ

هو الهدف الاسمي حيث نحسب (كم ملليجرام؟ وكل كم ساعة؟) بناءً على وزن المريض وحالته الصحية لضمان افضل نتيجة علاجية

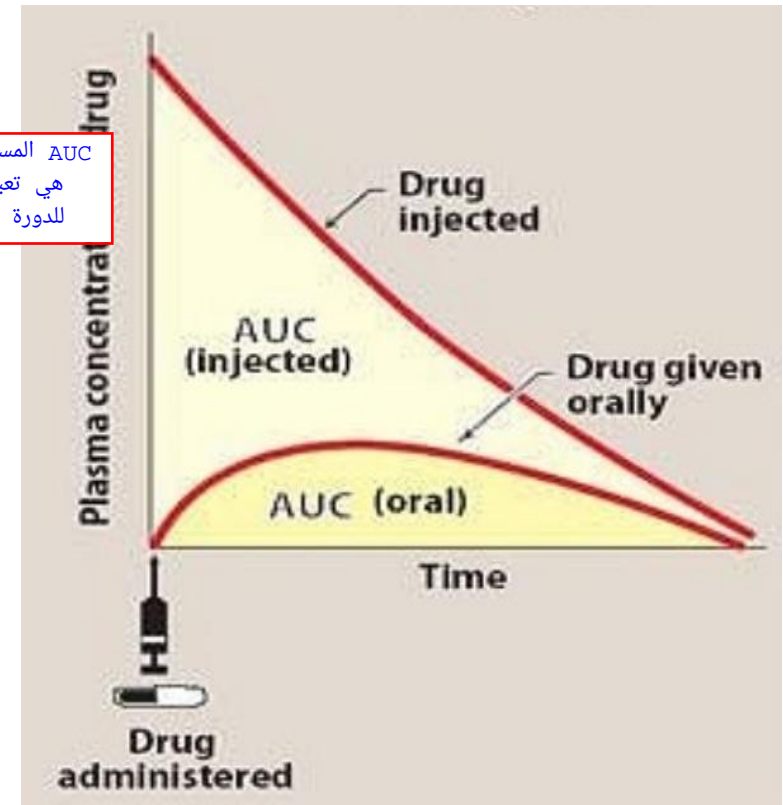
# Bioavailability measurements ⇒ amount the drug that reach systemic circulation

- Bioavailability is usually assessed by determining the area under the plasma concentration–time curve (AUC)


AUC المساحة المظللة بالكامل تحت هذا المنحنى هي تعبر عن اجمالي كمية الدواء التي وصلت للدورة الدموية وبقيت فيها لفترة زمنية معينة

- The most reliable measure of a drug's bioavailability is AUC.
- Blood drug concentration in human following the administration of the drug by oral or IV routes. A comparison of the behaviour of orally administered drug with that of IV administered drug in human.

الحقن الوريدي: يعتبر المرجع لان الدواء يذهب للدم مباشرة بنسبة 100% (اي ان التوافر الحيوي له يساوي واحد)  
الاقراص: تفقد جزءا من قوتها في المعدة او الكبد  
الحسبة: نقسم المساحة الخاصة بالفم على المساحة الخاصة بالوريد لنعرف النسبة المئوية التي وصلت فعليا للدم



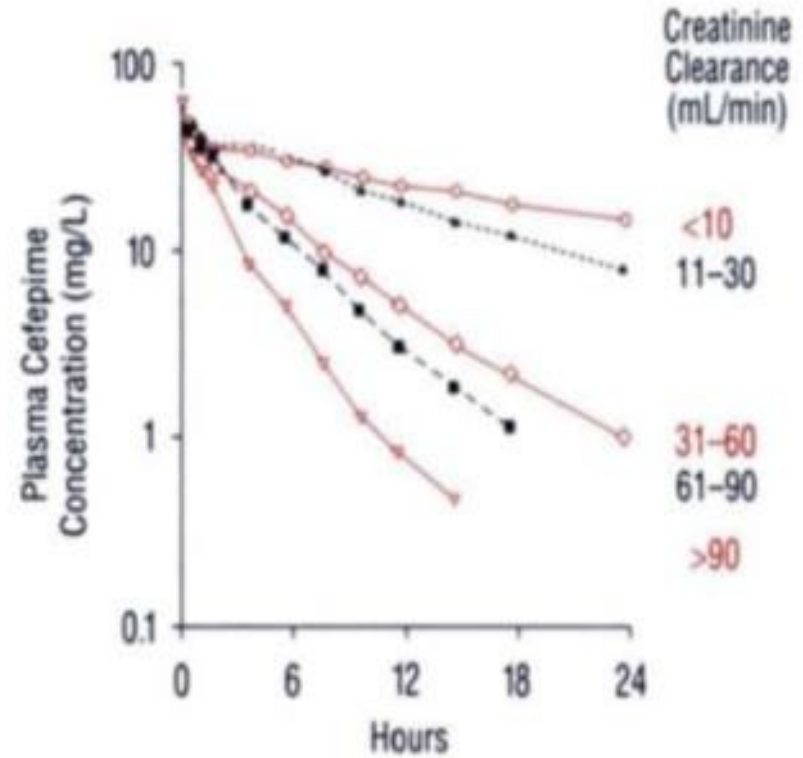
# Bioavailability

- **Bioavailability:** is the fraction <sup>الجزء</sup> of administered drug that reaches the systemic circulation.
- Bioavailability is expressed <sup>يُجرى عنه</sup>  as the fraction of administered drug that gains access to the systemic circulation **in a chemically unchanged form.**
- **For example:** if 100 mg of a drug are administered orally and 70 mg of this drug reach the systemic circulation, then the bioavailability is 0.7 or 70%.

# Effects of physiological and pathological conditions on drug disposition and absorption

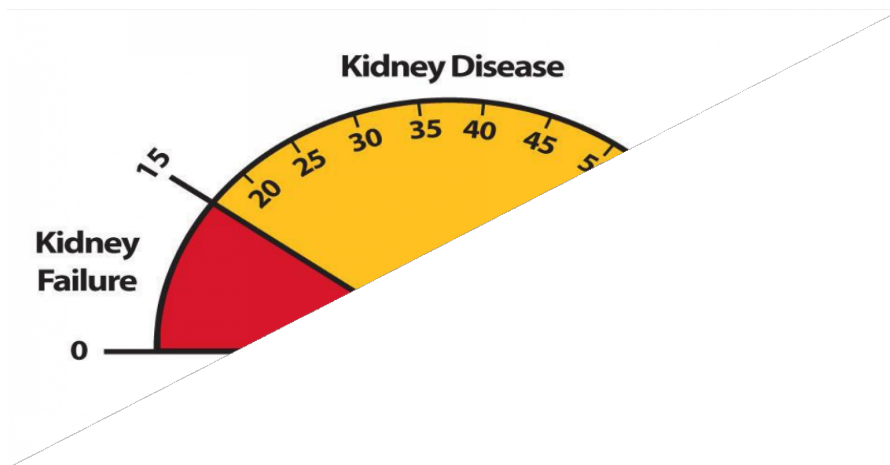
$$C = \frac{\text{mass}}{\text{volume}}$$

- **Plasma conc-time profile of cefepime after 1000 mg infusion d.b.v.**



سلوك الدواء في الرسم	حالة الكلى	قيمة تصريف الكرياتينين (CrCl)
المنحنى بهبط بسرعة كبيرة (الجسم يتخلص من الدواء بفعالية).	طبيعية جداً	أكبر من 90 (>90)
الدواء يخرج ببطء أكبر قليلاً.	قصور بسيط إلى متوسط	من 31 إلى 90
المنحنى شبه أفقي؛ الدواء يبقى بتركيز عالٍ لفترة طويلة جداً.	فشل كلوي حاد	أقل من 10 (<10)

نركز على انه التوافر الحيوي ما يتغير وإنما عمر النصف للدواء ان زاد وتراكم الدواء بسبب فشل الكلى في تصريف الدواء ← التوافر الحيوي هو الجزء الذي وصل إلى الدم.



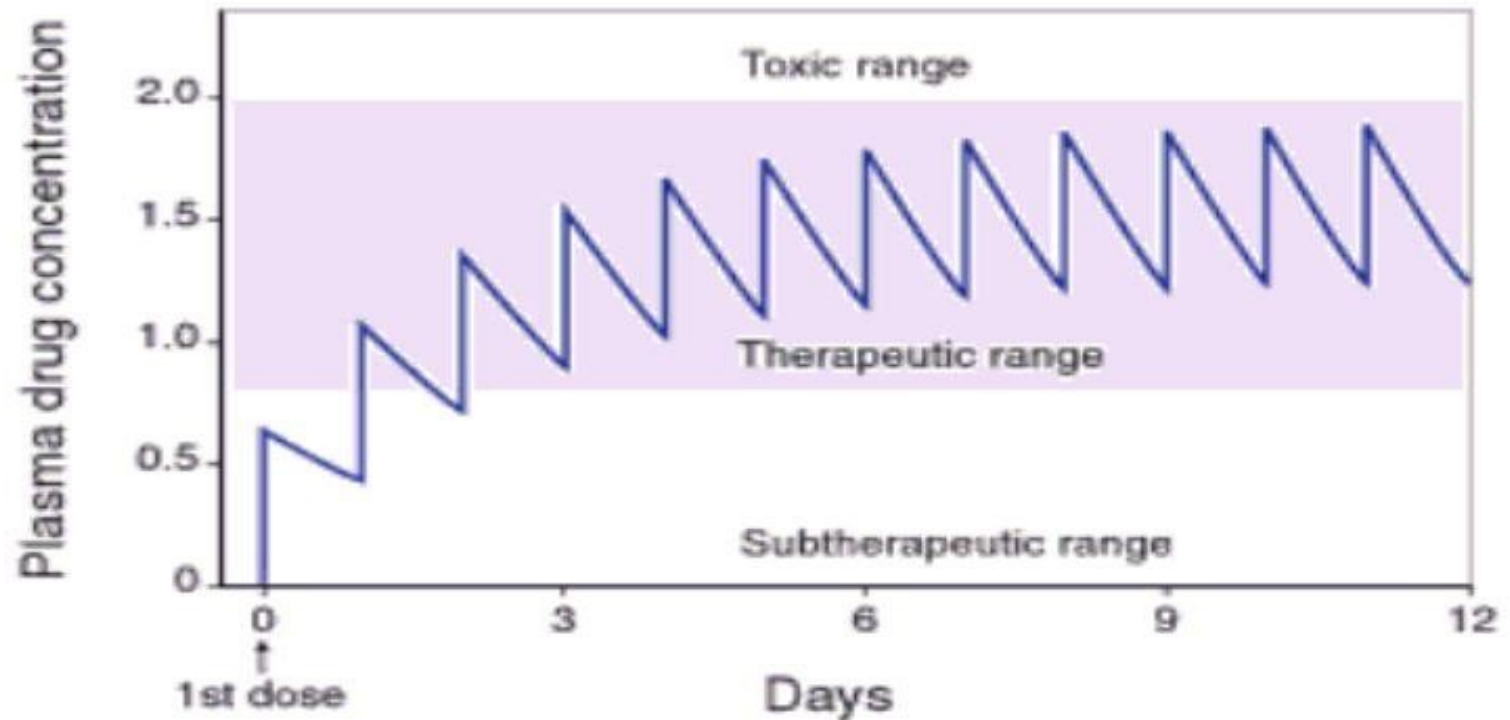
<b>GFR category</b>	<b>GFR (mL/min/1.73 m<sup>2</sup>)</b>	<b>Terms</b>
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.

**Note:** Data from KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl.* 2013;3:1–150.<sup>2</sup>

**Abbreviation:** GFR, glomerular filtration rate.

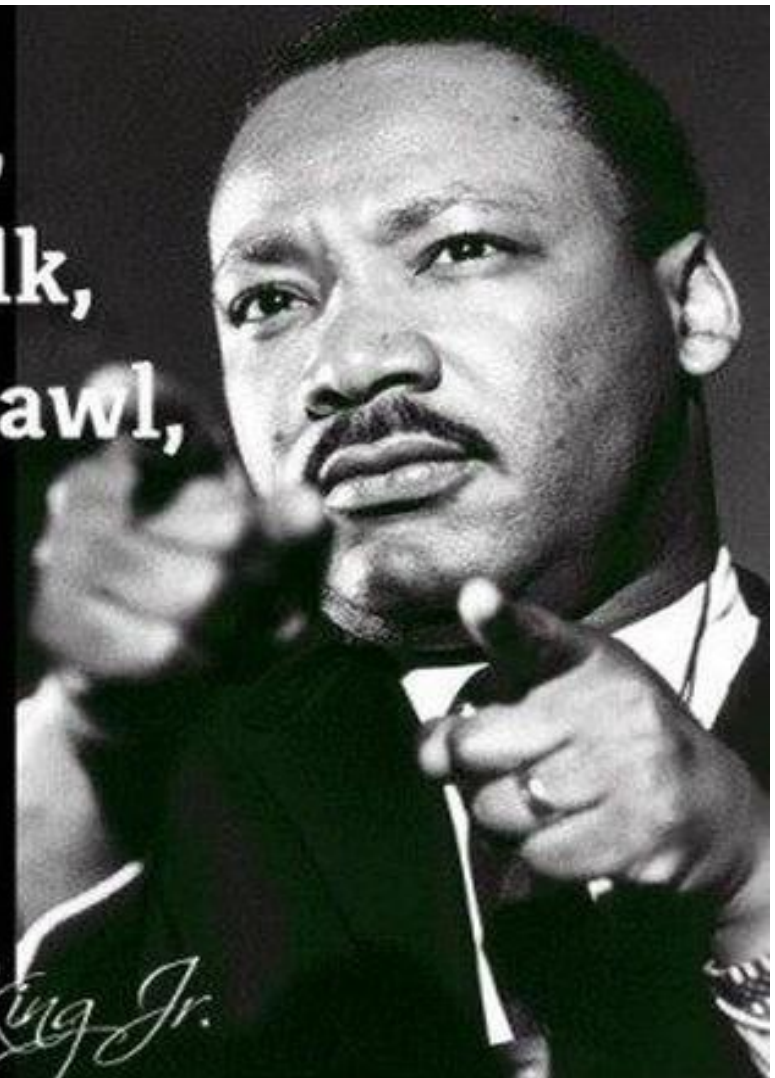
# Applications of pharmacokinetics



**Using pharmacokinetic parameters to design a dosing regimen and thus provide the most effective drug therapy**

If you can't fly then run,  
if you can't run then walk,  
if you can't walk then crawl,  
but whatever you do  
you have to  
keep moving forward.

*- Martin Luther King Jr.*



***THANK YOU***

***ANY QUESTIONS?***

