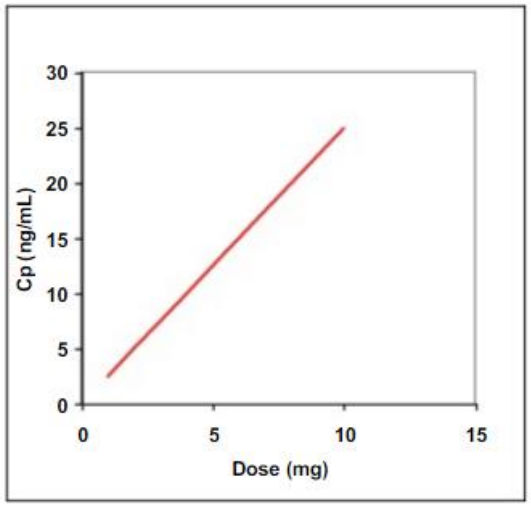
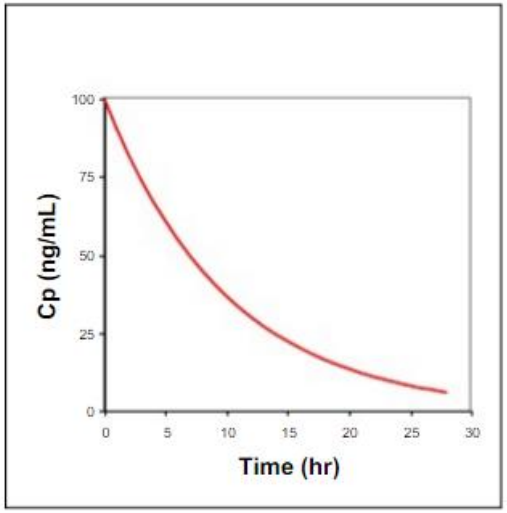
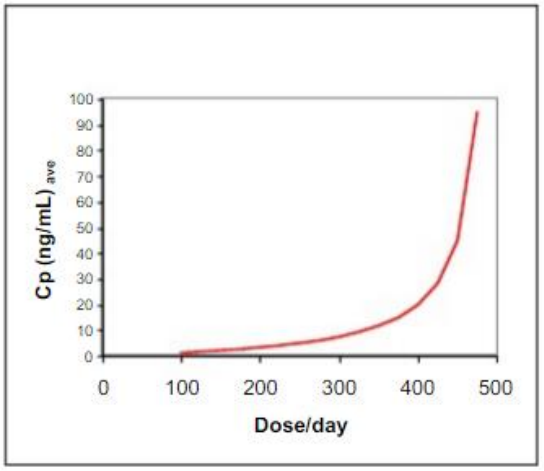
4. NON-LINEAR PHARMACOKINETICS

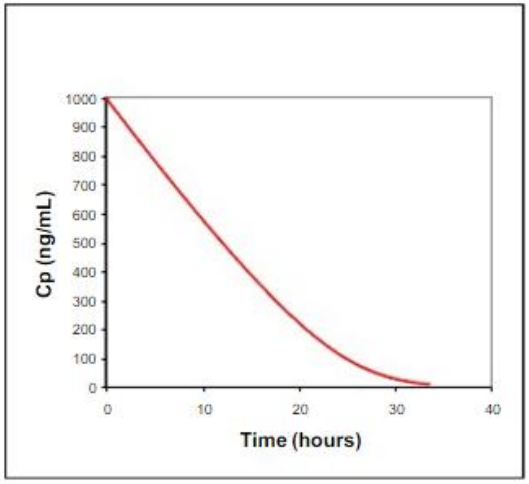




Linear PK:

Drug concentration that results from the dose is proportional to that dose and the rate of elimination of the drug is proportional to the concentration

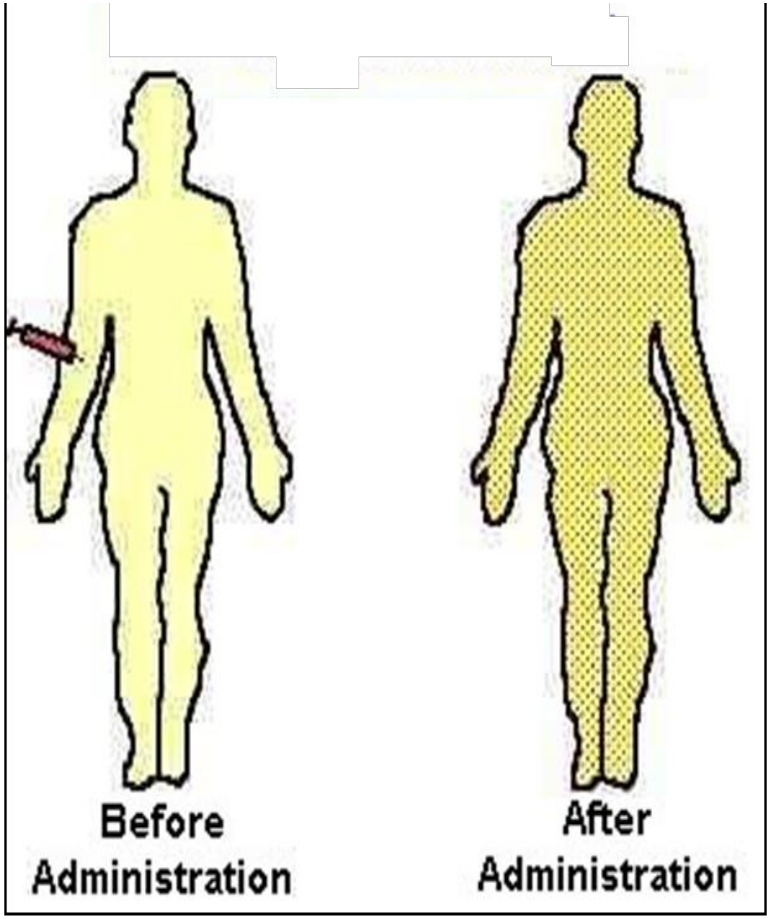


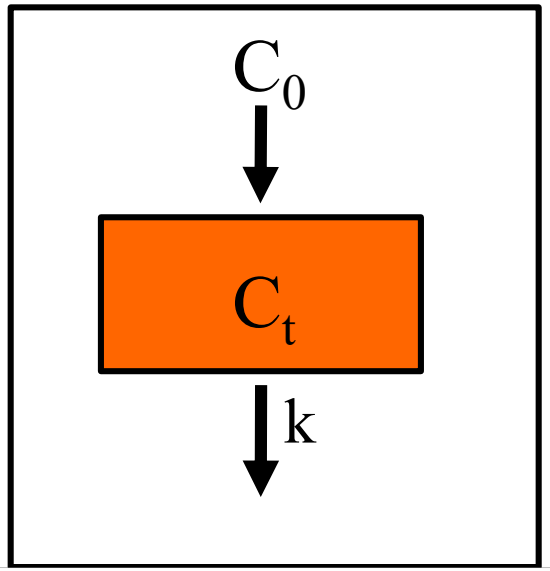


Non-linear PK:

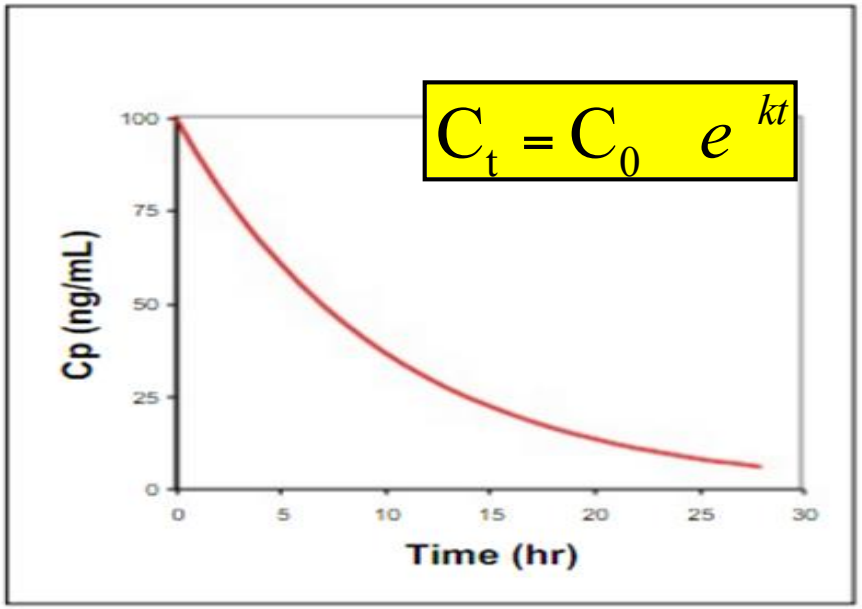
Drug concentration that results from the dose is not proportional to that dose and/or the rate of elimination of the drug is not proportional to the concentration

4.1 Linear pharmacokinetics





One compartment model

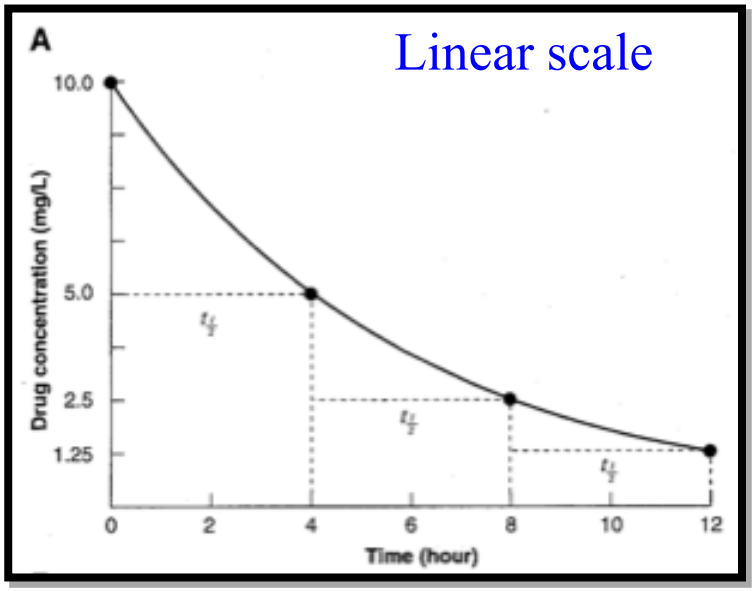


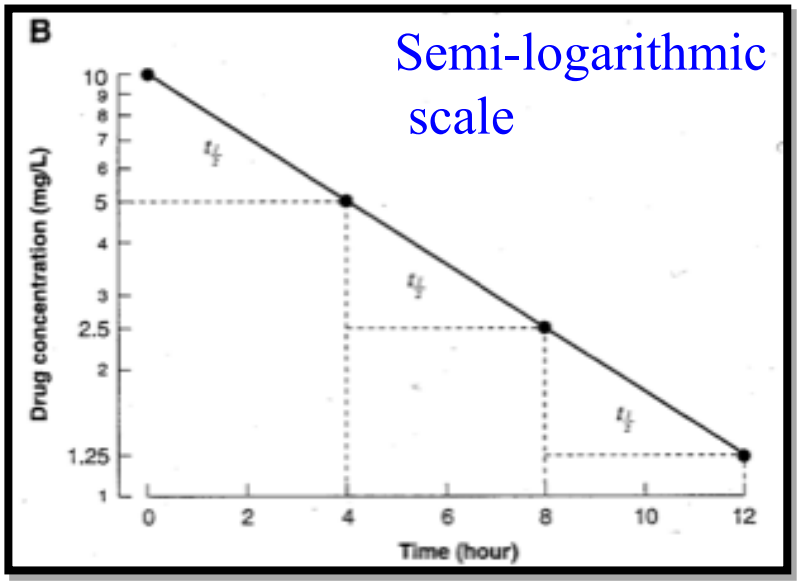
What is half-life ?

Definition : Half-life is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half.

It is the reciprocal function of the elimination rate constant.

$$C = \frac{1}{2}C_0 \Rightarrow \frac{C}{C_0} = e^{kt} = \frac{1}{2} \Rightarrow \ln\frac{C}{C_0} = \ln\frac{1}{2} = \ln 2 = kt_{1/2} \Rightarrow t_{1/2} = \frac{\ln 2}{k}$$





What determines half-life ?

- Half-life and elimination rate constant are determined by both clearance and volume of distribution.

$$t_{1/2} = \frac{\ln 2 \quad V}{CL}$$

Effects of CL and V in determining half-life

Drug	Clearance (L/hour)	Volume of distribution (L)	Half-life (hours)
Ethosuximide	0.7	49	48.0
Flucytosine	8.0	49	4.2
Digoxin	7.0	420	40.0
Morphine	63.0	280	3.0
Haloperidol	46.0	1,400	20.0
Chloroquine	45.0	12,950	200.0

Why is half-life important ?

Half-life is a major determinants of :

- *The duration of action after a single dose.*
- *The time required to reach steady state with chronic dosing.*

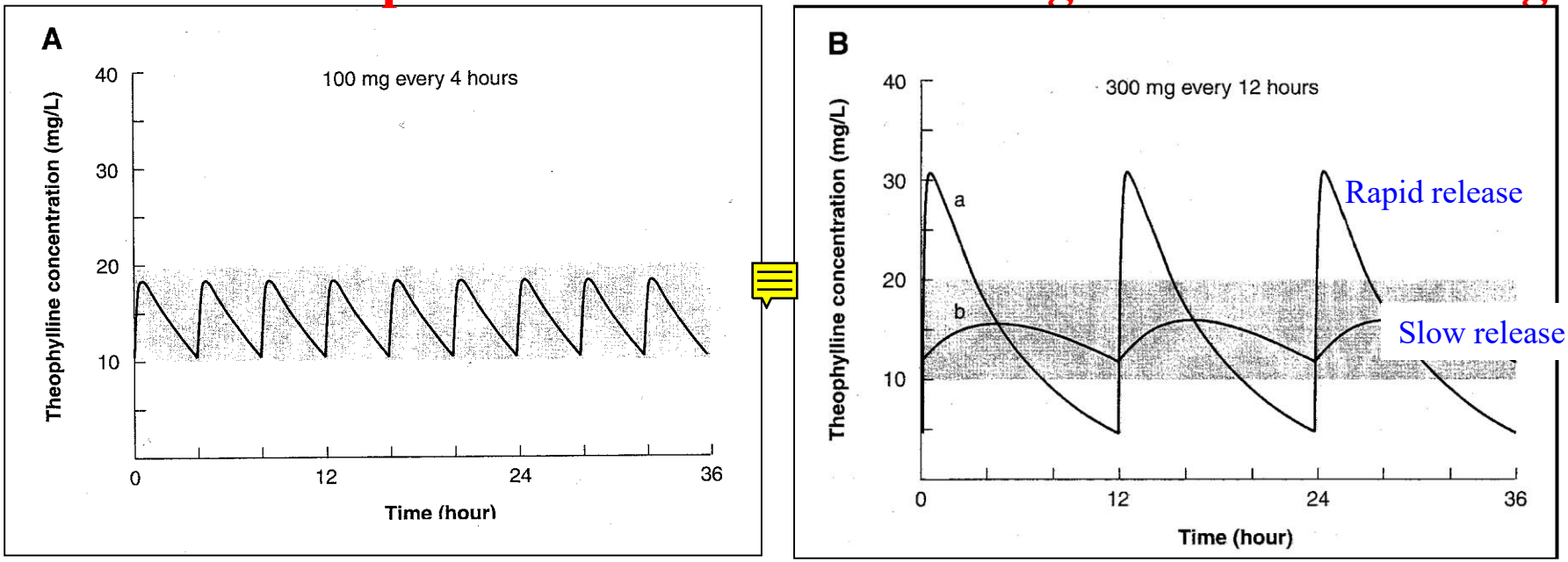
Accumulation to steady state

Number of half-lives since starting constant rate dosing	Plasma concentration as a percentage of eventual steady state concentration (%)
1	50
2	75
3	87.5
4	93.75
5	96.875

Why is half-life important ?

• *The dosing frequency required to avoid too large fluctuations in plasma concentration during the dosing interval.*

Fluctuation in plasma concentration during intermittent dosing



- The half-life determines the duration of action after a single dose of drug, the time taken to reach steady state with constant dosing and the frequency with which doses can be given.

N'écrasez pas les médicaments

SANTÉ Cela les rendrait inefficaces

Faire avaler certains cachets à des enfants ou à des personnes souffrant de troubles de la déglutition ou de troubles psychocomportementaux relève parfois de la quadrature du cercle. Pour pallier cette difficulté, les familles et le personnel médical ont trouvé la parade : il suffit de les écraser ! Une pratique tellement courante qu'au CHU de Rouen, elle a été à l'origine d'une épidémie de tendinites chez les infirmières ! Une épidémie qui a poussé le Dr Caussin et ses collègues du département de pharmacie à mener l'enquête.

Pas facile de faire avaler un médicament à un enfant. L'écraser ? C'est tentant. Mais contre-indiqué. © DR.

Leur étude a permis de constater que les médicaments de 30 à 40 % des patients hospitalisés en gériatrie étaient administrés sous forme de poudre. Soit les comprimés étaient écrasés, soit les gélules étaient ouvertes et dans certains cas, les poudres de tous les médicaments étaient mélangées avant d'être administrées aux patients. Rien de bien grave en apparence... Sauf que *« dans 42 % des cas, la forme galénique n'autorisait pas l'écrasement des médicaments »*, expliquent les auteurs de l'étude.

Pourtant, si on suit le trajet d'un médicament dans notre organisme, on constate qu'il est, au bout du compte, réduit en bouillie. Pourquoi l'écraser est donc une si mauvaise idée ? *« Lorsqu'on écrase un médicament, on le mélange ensuite avec un aliment en fonction des goûts du patient. Cet aliment varie sur le plan chimique (pH) et en température. On peut, par exemple, le mélanger à une soupe ou à un yaourt »*, explique le Dr Jean Doucet, gériatre au CHU Rouen. Or ces paramètres influencent la manière dont le principe actif – la partie du médicament qui possède l'effet thérapeutique - agit.

En outre, il est difficile de s'assurer qu'il ne reste pas de petites quantités de médicaments collées sur les parois du récipient qui a servi au pilonnage. *« Le principal danger du pilonnage, c'est l'inefficacité du médicament. Soit parce qu'en l'écrasant vous en laissez un peu de côté, soit parce que le principe actif du médicament ne supporte pas d'être exposé à la lumière ou à l'air »*, explique Elise Rémy, de l'Observatoire du médicament de Haute-Normandie.

Celui qui écrase risque aussi

Notez que le pilonnage n'est pas sans conséquence pour celui ou celle qui écrase le médicament ! S'il le fait sans gants et sans masque, il s'expose à un risque d'allergie ou de réaction au niveau respiratoire !

Que convient-il de faire alors quand votre bambin refuse catégoriquement de prendre ses cachets ? Jeter un œil sur la posologie et, si rien n'y est indiqué, demandez conseil à votre médecin/pharmacien. Il est souvent possible de remplacer le médicament en cachet par un équivalent vendu sous forme de poudre ou de gouttes. ■ **ELISE DUBUISSON**

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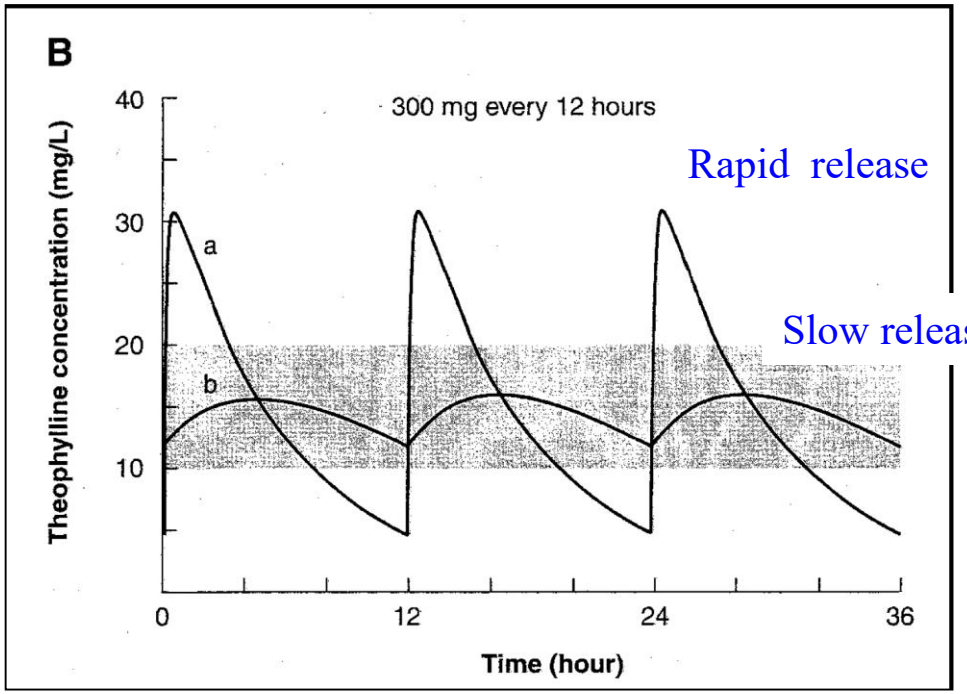
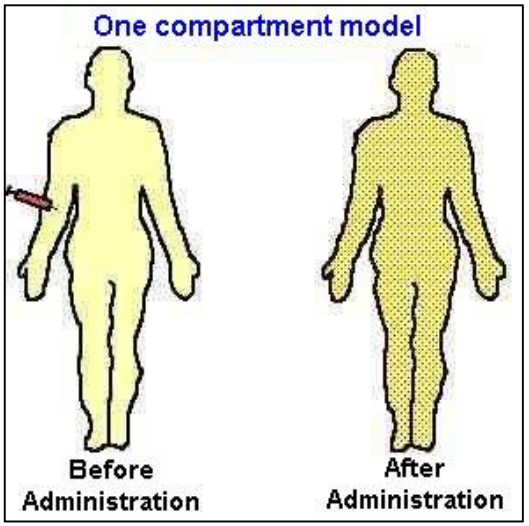
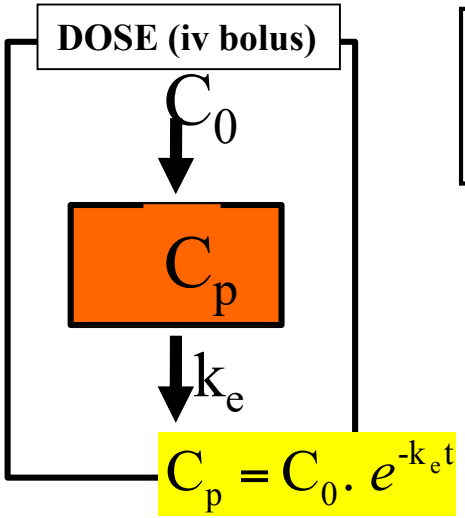


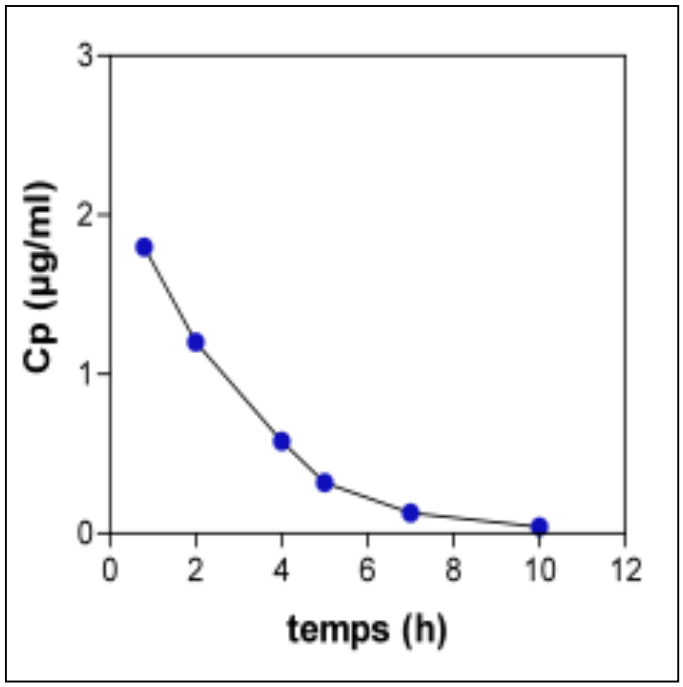
Compartment Models

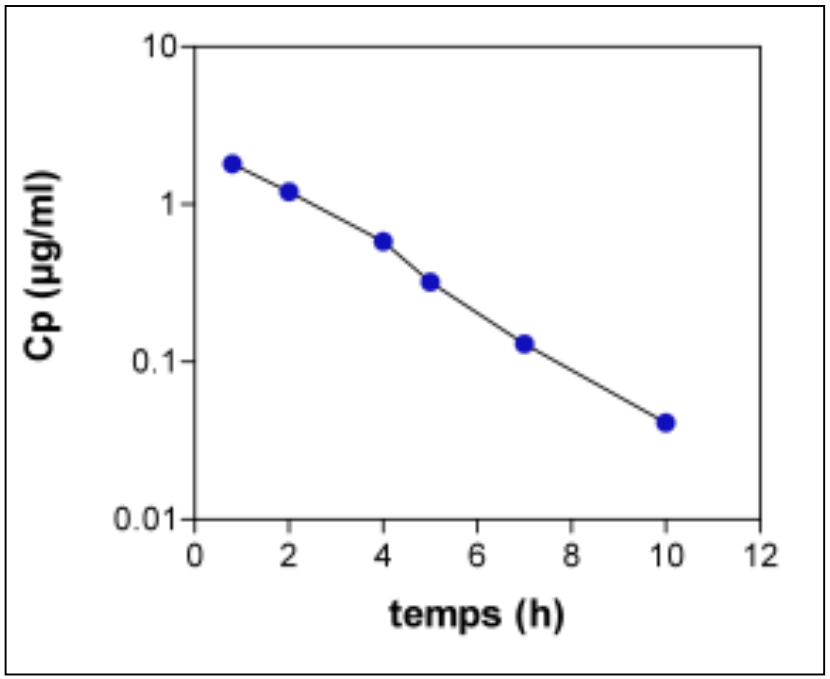




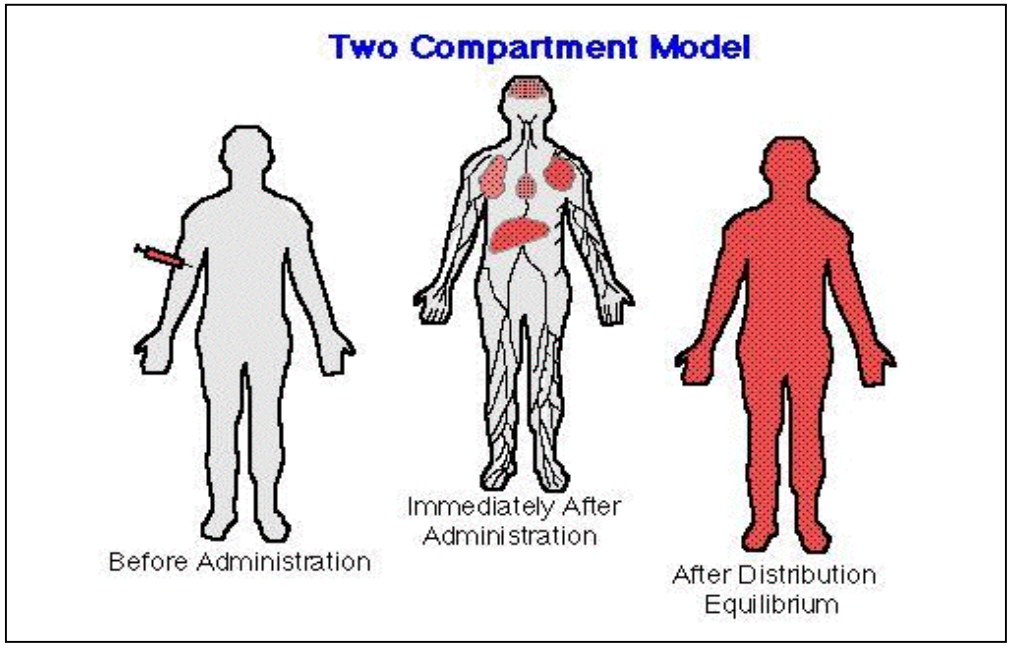
One compartment model

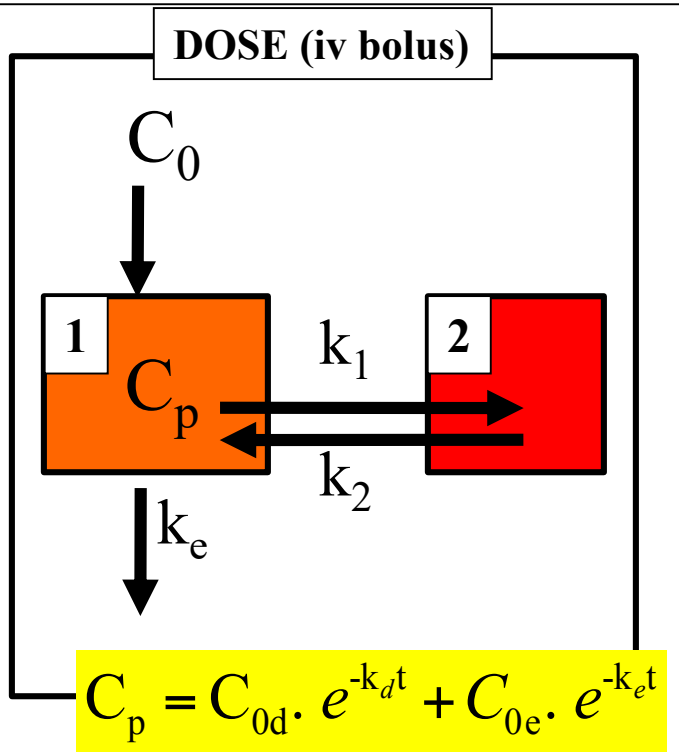
Example:
Aminoglycosides

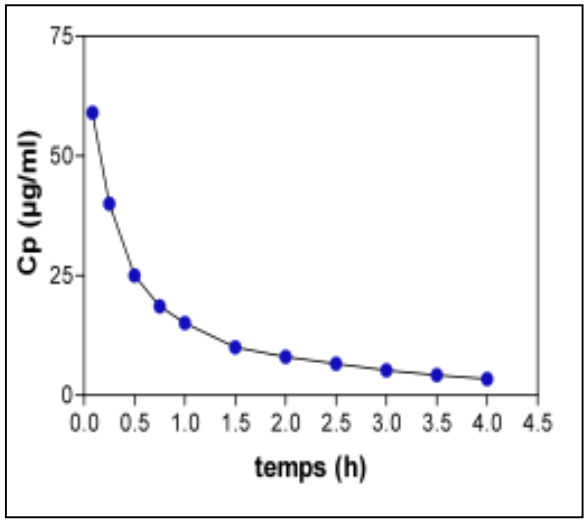


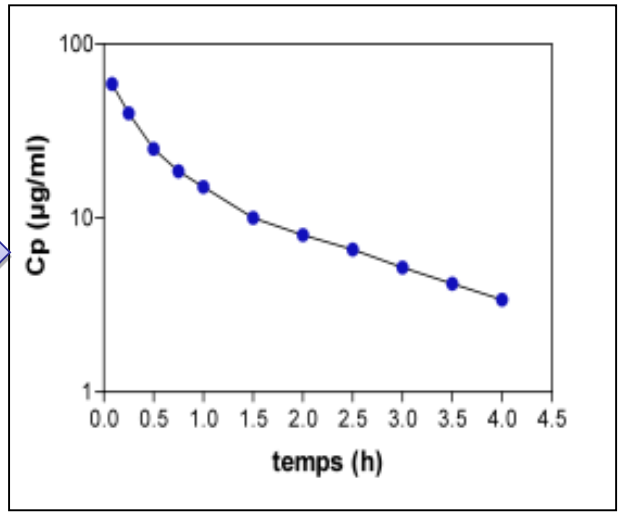


Compartment Models



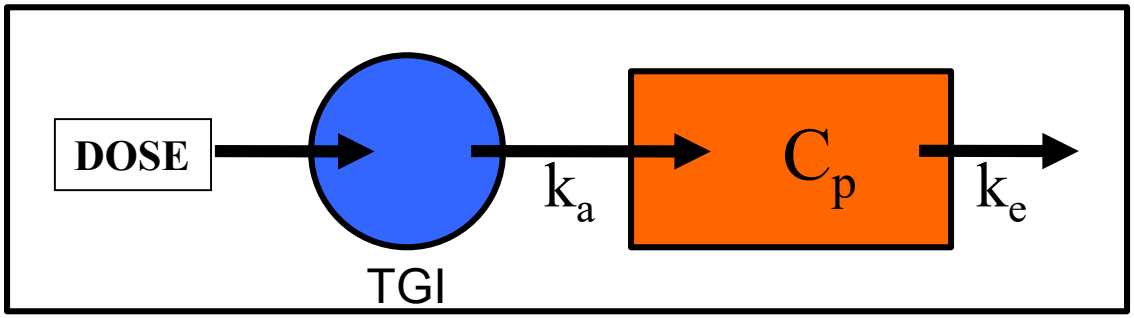






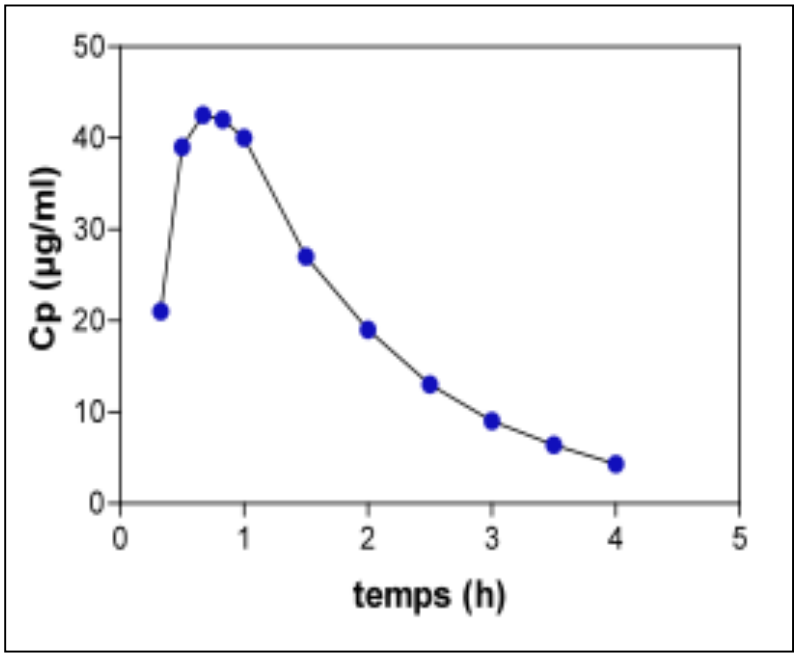
Example:
Vancomycin

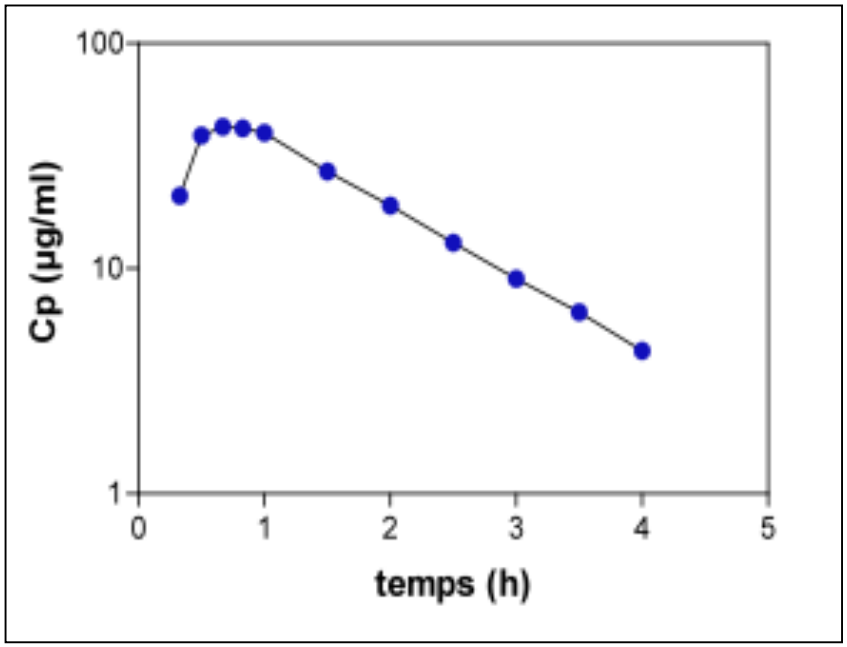
Compartment Models



$$C_p = A \times \left(e^{-k_e \cdot t} - e^{-k_a \cdot t} \right)$$

$$A = \frac{k_a \cdot F \cdot DOSE}{V\left(k_a - k_e\right)}$$





Questions?

- ***Half-life :***
  a) is the time taken for the plasma concentration to fall by half
  b) has units of 'per hour'
  c) is the time taken for the amount of drug in the body to fall by half
  d) decreases as elimination rate constant increases
  e) increases as the elimination rate constant increases

- ***Half-life :***
  a) increases as clearance increases
  b) decreases as volume of distribution increases
  c) decreases as clearance increases
  d) increases as volume of distribution increases
  e) increases as elimination rate constant decreases

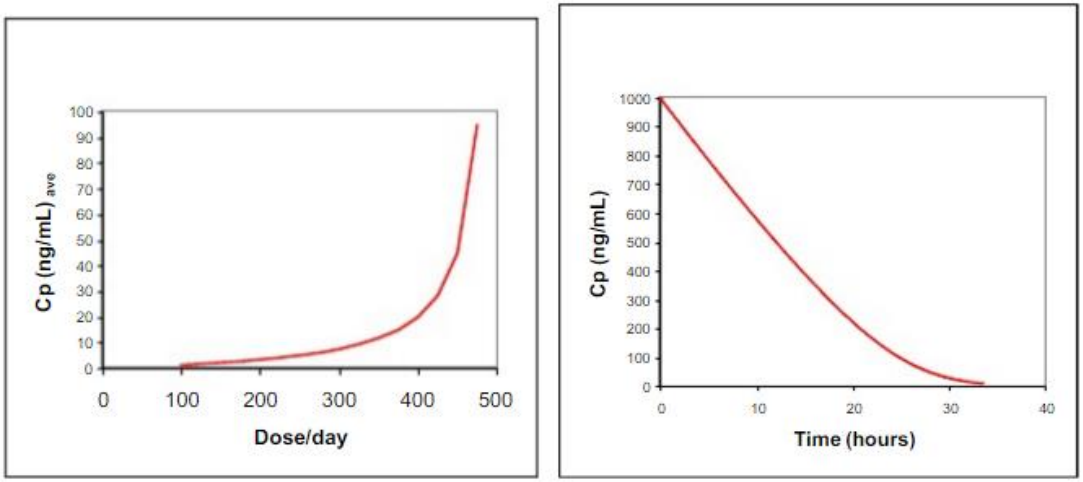
- ***Half-life determines :***
  a) the loading dose
  b) the time to reach steady state
  c) the drug concentration at steady state during constant dosing
  d) the duration of action after a single dose
  e) the fluctuation in plasma drug concentration during a dosing interval

- ***After a single dose of drug which has a half-life of 12 hours, what percentage of the dose is still in the body after 1 day ?***
  a) 87.5 % b) 75 % c) 50 % d) 25 % e) 12.5 %

- ***During a constant rate intravenous infusion of a drug with an elimination rate constant of 0.173 per hour, the plasma drug concentration will be what percentage of steady state after 16 hours ?***
  a) 25 % b) 50 % c) 75 % d) 87.5 % e) 93.75 %

4.2. Non-linear kinetics

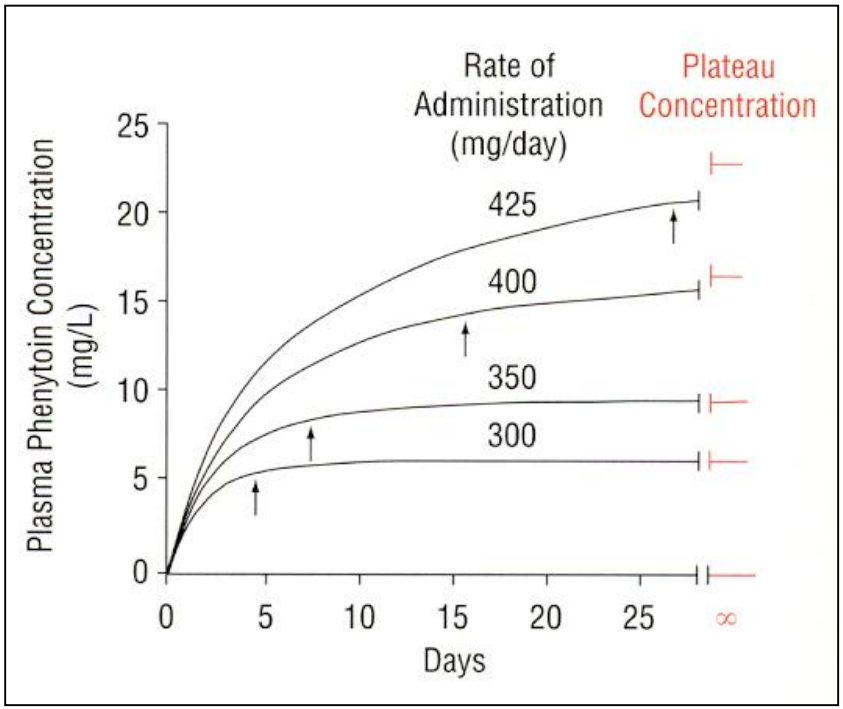
- Doubling the dose usually doubles the drug concentration because drug elimination rate is proportional to drug concentration, but not for all drugs.

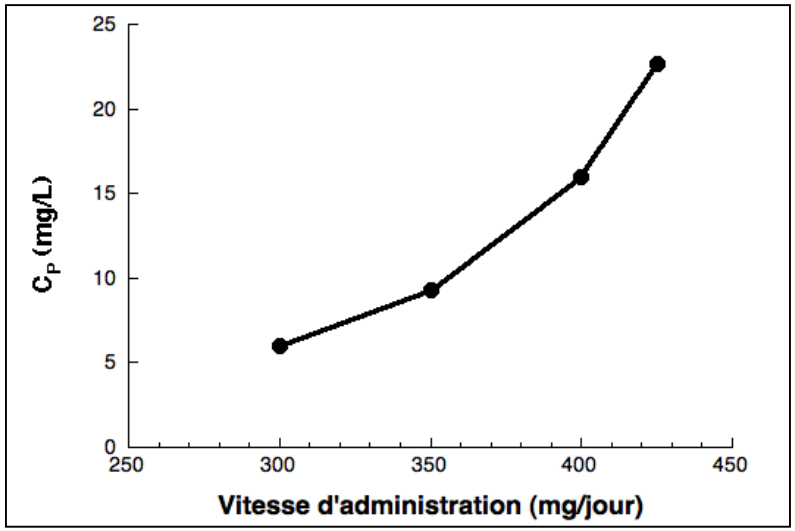


When a dose of a drug is increased, we expect that the concentration at steady state (CSS) will **increase proportionately**. However, for some drugs, the plasma drug concentration changes either more or less than would be expected from a change in dose rate. This is known as ***non-linear*** pharmacokinetic behaviour and can cause problems when adjusting doses.

Non-linear pharmacokinetics (Example 1)

Phenytoin



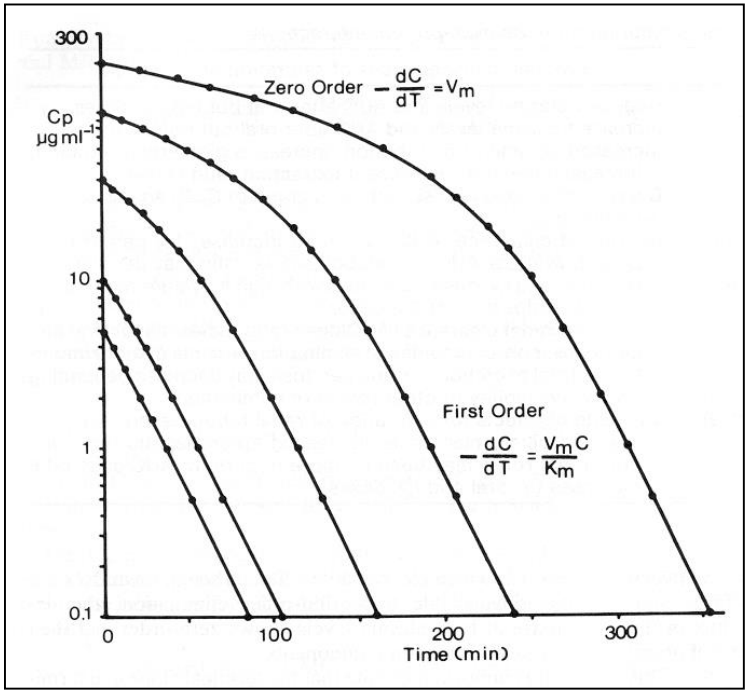


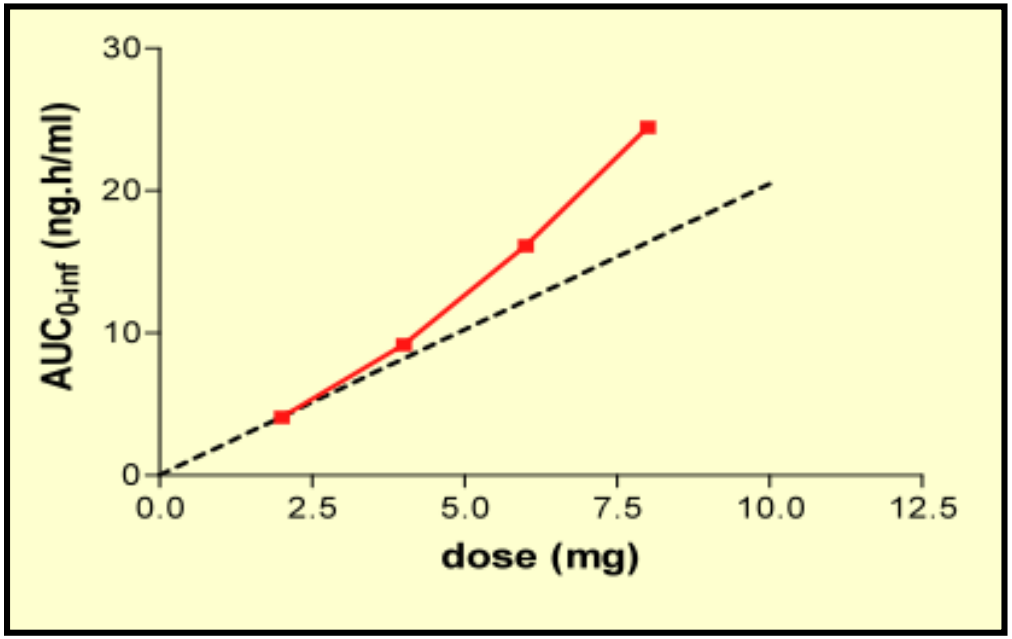
Non-linear pharmacokinetics (Example 2)

Salicylic acid

Dose (mg/kg)	5	10	40	100	200
AUC (µg.min/ml)	115	254	1614	7020	24000
CL (ml/min/kg)	43.5	39.4	24.8	14.2	8.3

$$\text{Clearance} = \frac{\text{dose}}{\text{AUC}}$$





What causes non-linear pharmacokinetic behaviour ?

For linear pharmacokinetics:

$$C_{SS} = \frac{F \quad \text{dose rate}}{CL}$$

For low hepatic extraction ratio drugs : $CL = fu \quad CL_{int}$

$$C_{SS} = \frac{F \quad \text{dose rate}}{fu \quad CL_{int}}$$

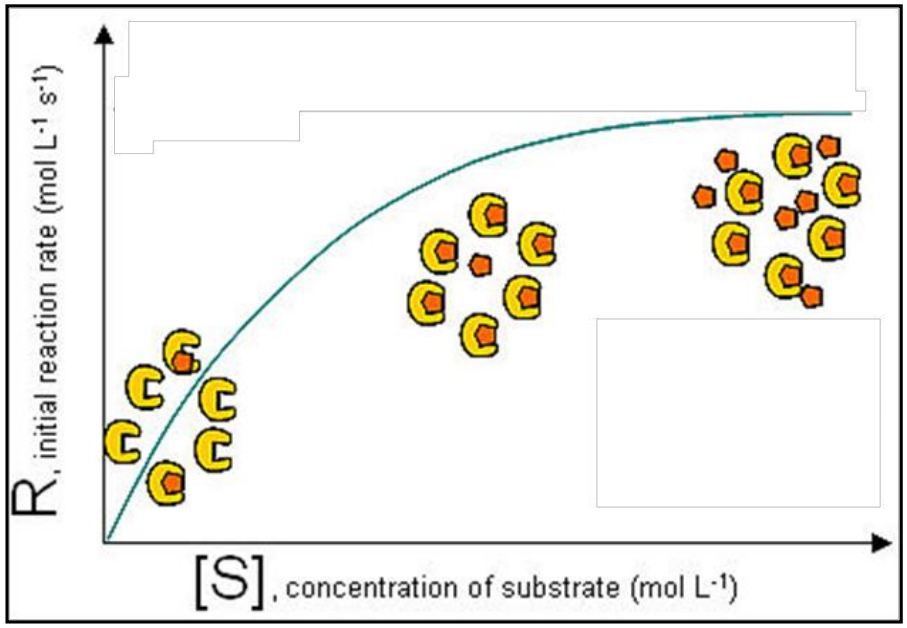
$$CL_{int} = \frac{V_{max}}{K_m}$$

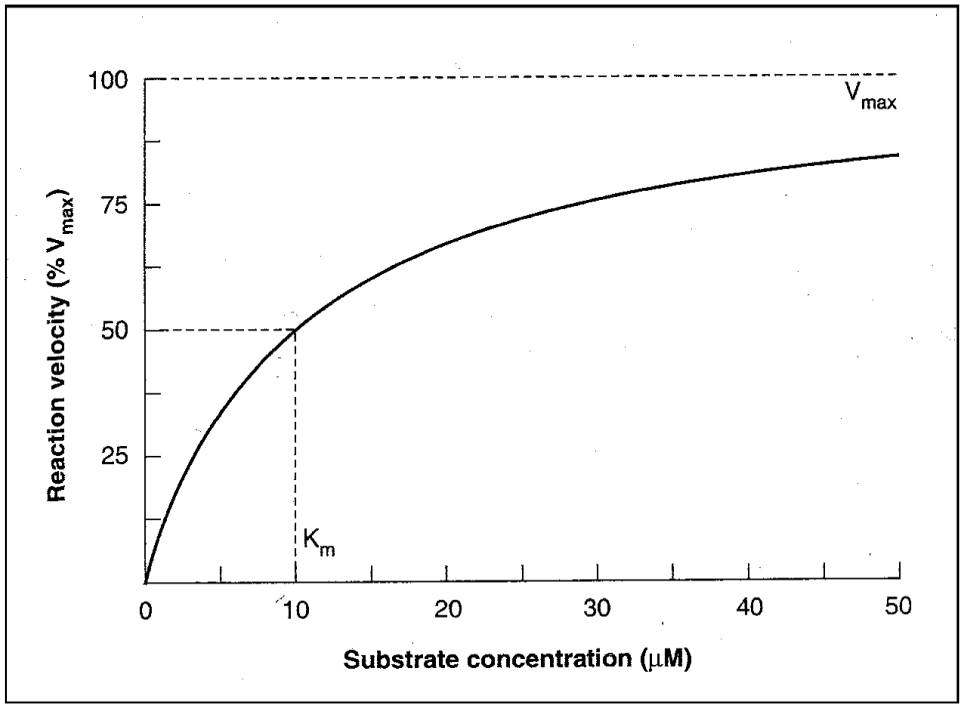
As F, fu and CL_{int} usually do not change with drug concentration, **C_{ss} is directly proportional to dose rate**. However, there are some situations where this predictable relationship breaks down due to **dose dependency of fu and/or CL_{int}.**

Saturation of drug metabolism causing a change in intrinsic clearance

Kinetics of drug-metabolising enzymes

$$E + S \rightleftharpoons ES \rightleftharpoons E + P$$





$$v = \frac{V_{max} * [S]}{K_m + [S]}$$

Saturation of drug metabolism causing a change in intrinsic clearance

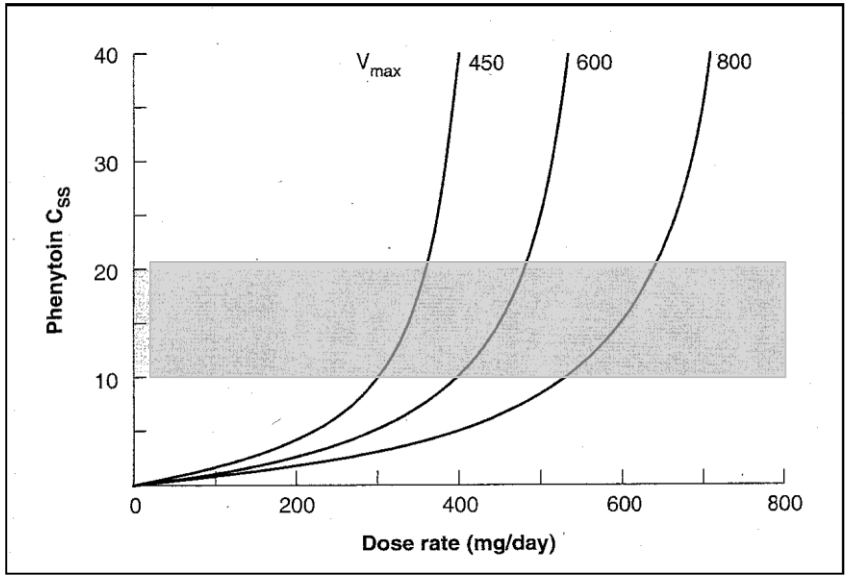
- Under non-saturating conditions

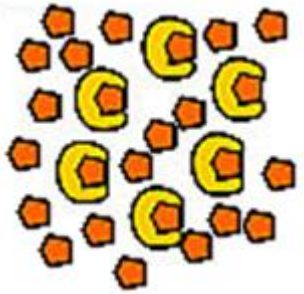
$$C_{SS} = \frac{F \quad \text{dose rate}}{fu \quad CL_{int}}$$

$$CL_{int} = \frac{V_{max}}{K_m}$$

$K_m >> C$

- Under (over-) saturating conditions:

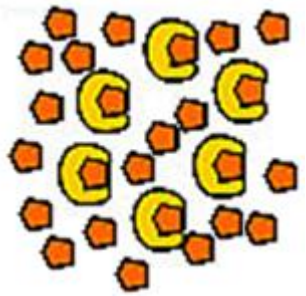




$$CL_{int} = \frac{V_{max}}{K_m + C}$$

Saturation of drug metabolism causing a change in intrinsic clearance

- The metabolism of drug in the liver is carried out by a variety of enzymes such as cytochrome P450 and N-acetyltransferase.
- Saturation of drug metabolizing enzymes, or renal active secretion processes, causes larger than expected increases in drug concentration (both total and unbound) with increasing dose rate.
- Under such a regime small increases in dose rate can result in large increases in drug concentration and consequent toxicity.
- Drug impacted by the saturation of drug metabolism are phenytoin, ethanol, salicylate and, in some individuals, thephyilline.



Saturation of first-pass metabolism causing an increase in bioavailability

After **oral administration**, the drug-metabolising enzymes in the liver are exposed to relatively high drug concentrations in the portal blood during the absorption process. **For drugs such as alprenolol with high hepatic extraction ratios, an increased dose can result in saturation of the metabolising enzymes, and a decrease in intrinsic clearance**. **Steady state concentration then increases more than proportionately with dose!!!**. Other examples of drugs with saturable first-pass metabolism are tropisetron and paroxetine.

Saturation of renal secretion clearance

Renal drug clearance is the sum of filtration clearance plus secretion clearance minus reabsorption. **Clearance by glomerular filtration and tubular reabsorption are both pasive processes which are not saturable, but secretion involves saturable drug binding to an active transport mechanism and is thus saturable**. An example is pencilline G.

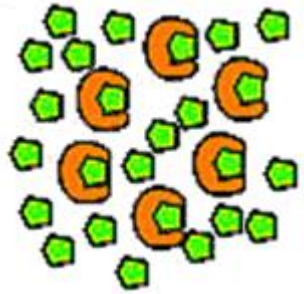
Saturation of protein binding sites causing a change in fraction of drug unbound in plasma

- The total concentration of albumin is 0.6mM and of α-acid glycoprotein is about 0.15mM.
- Ususally drug concentrations are well below those of the binding proteins
- In the rare case were the binding protein is (over-) saturated, the fu increases as drug concentration increases

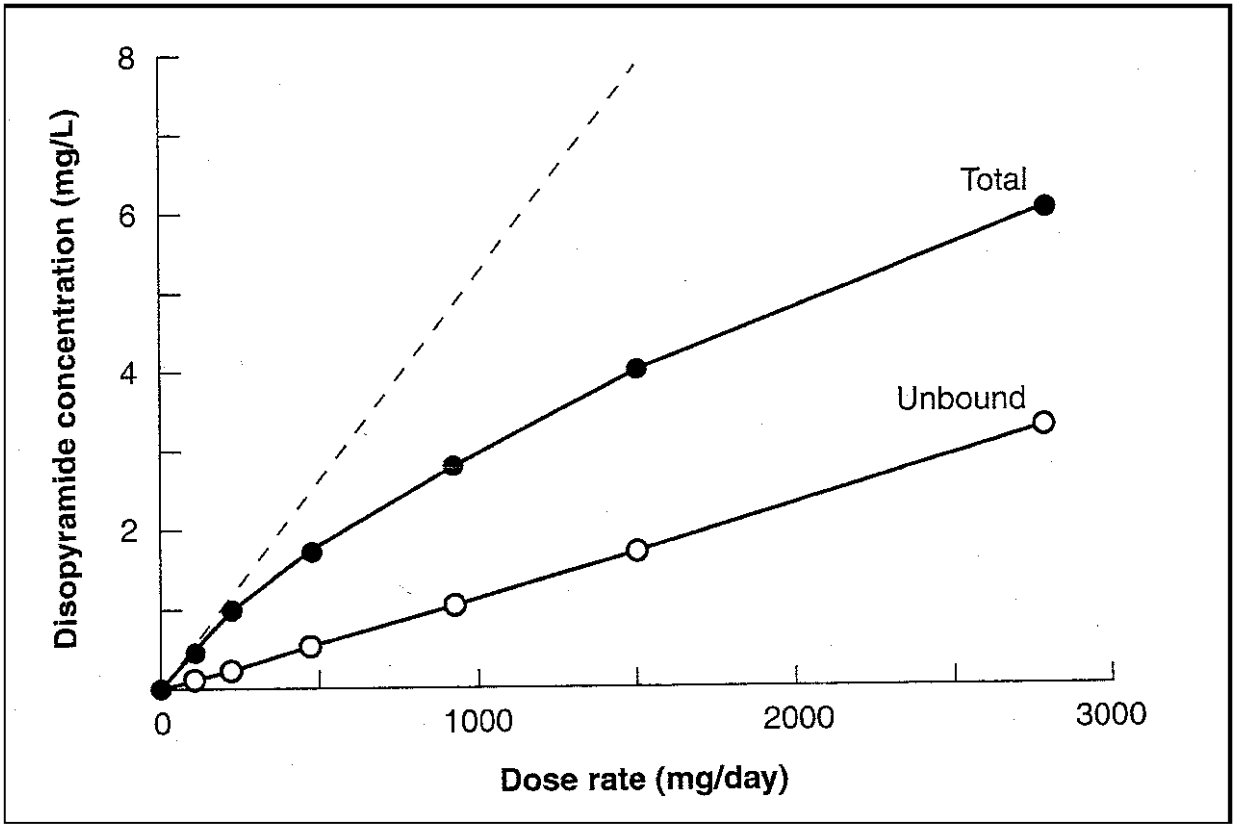
$$fu = \frac{1}{1 + K_a P_u}$$

K_a = affinity constant for protein binding
P_U = concentration of the unbound protein

Examples: Salicylate, phenylbutazone, diflunisal, and disopyramide



Saturation of protein binding sites causing a change in fraction of drug unbound in plasma



Questions ?

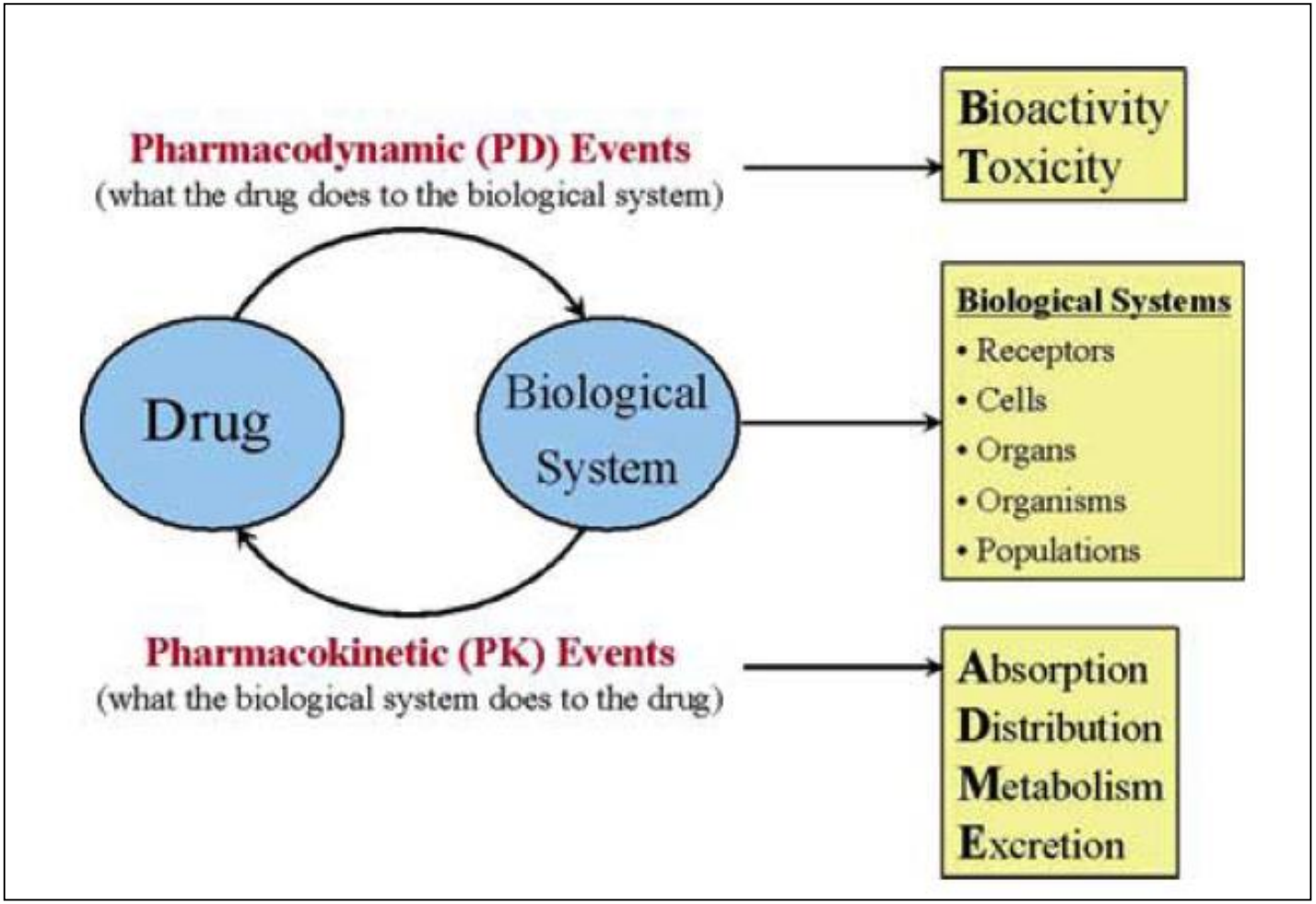
- ***The term linear pharmacokinetics means :***
  a) a plot of drug concentration versus time is linear
  b) half-life increases proportionately with dose
  c) a constant amount of drug is eliminated per unit time
  d) clearance is proportional to dose
  e) steady state drug concentration is proportional to dose

- ***Saturation of drug-metabolising enzymes occurs when :***
  a) drug concentration is similar to maximal reaction velocity
  b) the K_m is very high
  c) the drug concentration is above the K_m
  d) the maximal reaction velocity and K_m are similar
  e) the K_m is high compared to the drug concentration

- ***Saturation of protein binding occurs when :***
  a) the concentration of binding protein is high
  b) the affinity of the drug for the protein is high
  c) the drug concentration approaches the concentration of protein binding sites
  d) fraction unbound (fu) is low
  e) the concentration of protein binding sites is high compared to the drug concentration

- ***Which of the following processes are saturable and can result in non-linear pharmacokinetics ?***
  a) drug metabolism
  b) glomerular filtration
  c) protein binding
  d) renal tubular secretion
  e) renal tubular reabsorption

4.3. Pharmacodynamics : The concentration-effect relationship



What is pharmacodynamics?

To produce therapeutic or toxic effects, drugs interact with receptors in the body – the pharmacodynamic phase of drug action. The drug in the tissues, where drug-receptor interactions usually occur, is in equilibrium with the unbound drug in the plasma.

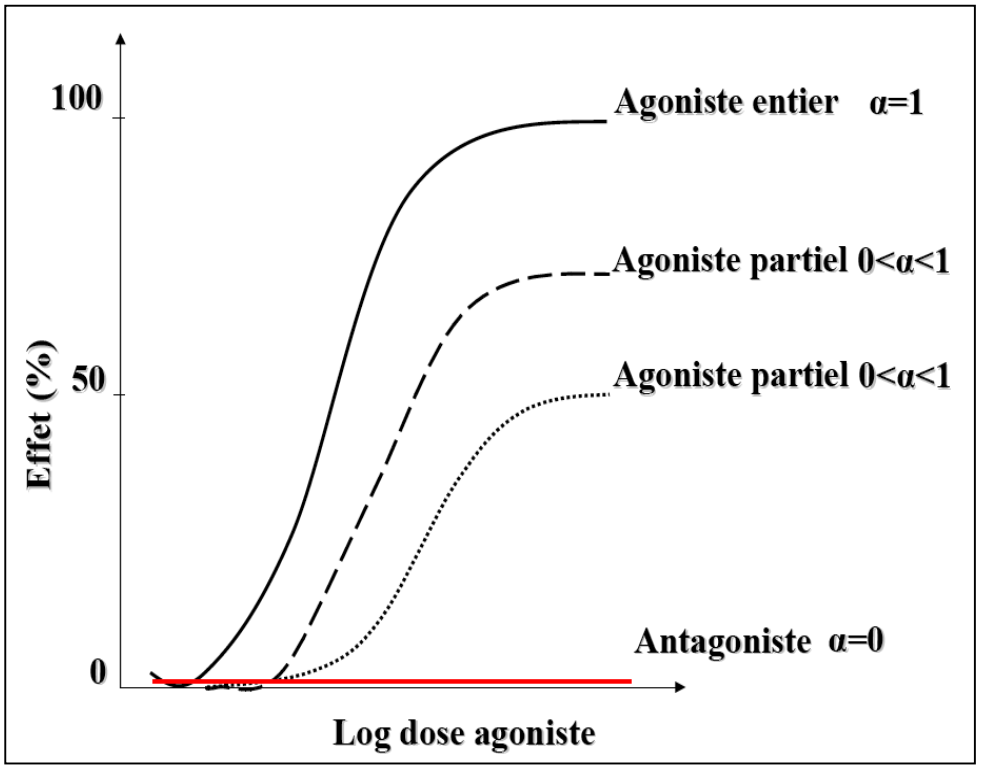
How do drugs produce effects ?

A drug which binds to a receptor and produces maximum effect is called a **full agonist**.

A drug which binds to a receptor and produces less than a maximal effect is called a **partial agonist**.

Drugs which bind but do not activate second messenger systems are called **antagonists**.

The agonists / antagonists



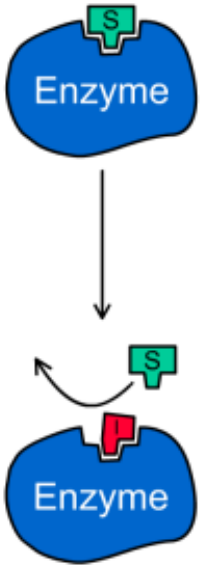
A drug which has the same (or less) comparable effect as the natural substrate is a **(partial) agonist**.

A drug which is blocking the binding site without having the effect of the natural substrate is an **antagonist**.

The response efficency is measured by a factor α, which is specific for each drug.

Antagonists can be classified in different types.

The antagonists

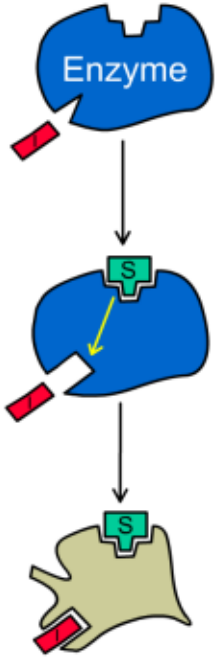


- **Antagonisme chimique** : correspondant à une interaction chimique de l'antagoniste avec l'agoniste indépendamment de toute interaction avec le récepteur.

- **Antagonisme compétitif** : correspondant à la fixation de l'antagoniste au site de liaison de l'agoniste.

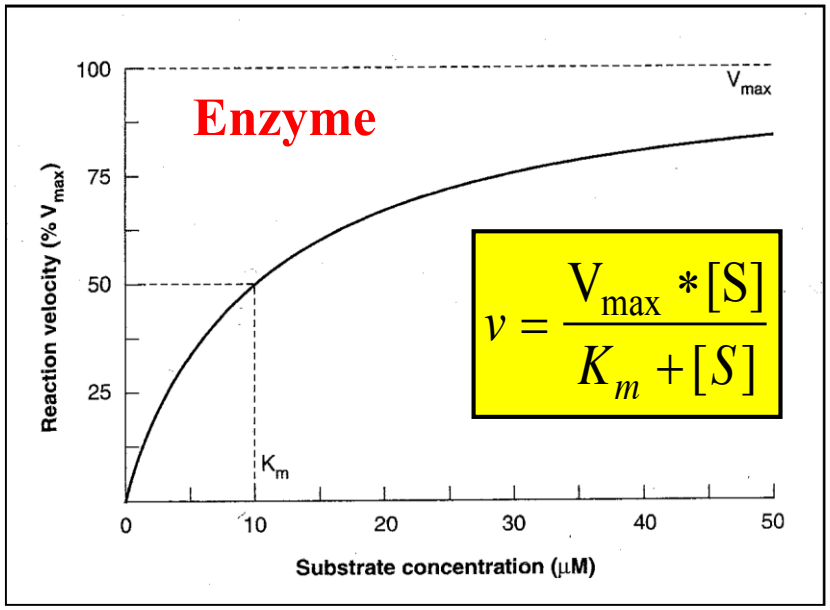
- **Antagonisme non compétitif** : correspondant à la fixation de l'antagoniste sur un site de liaison distinct du site de liaison de l'agoniste (effet de type allostérique).

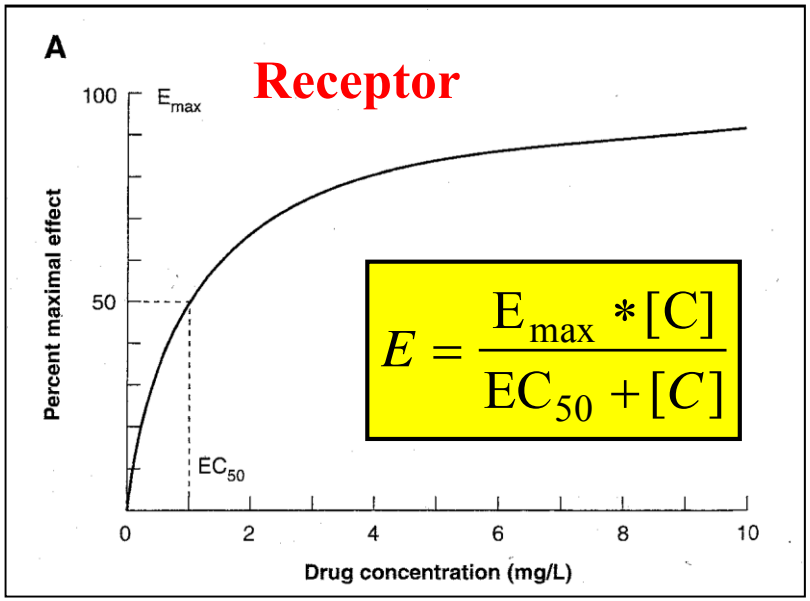
- **Antagonisme fonctionnel** : correspondant à une interaction résultant de processus biochimiques cellulaires distincts (par exemple sur une même cellule, l'agoniste d'un récepteur peut entraîner une contraction et l'agoniste d'un autre récepteur une relaxation; les deux agonistes ont des effets antagonistes)



Drug concentration-effect relationship

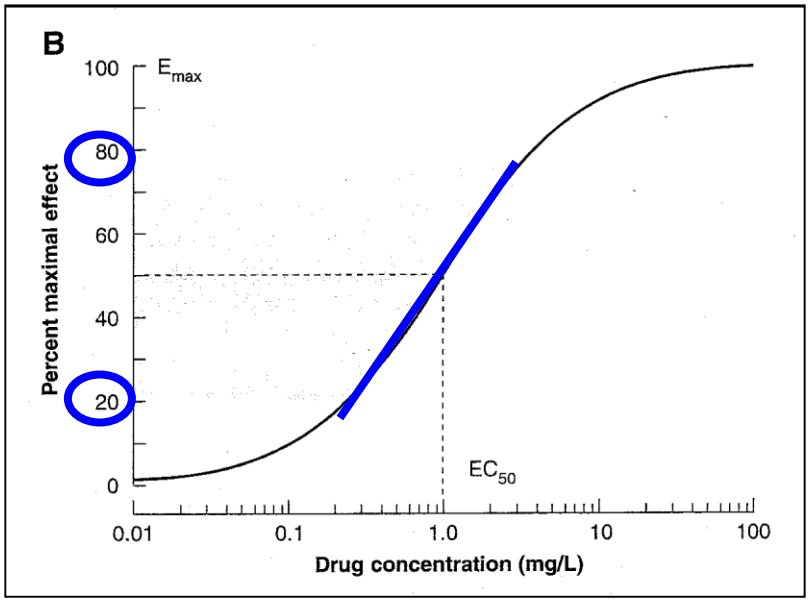
- The interaction of a drug with a receptor involves it binding to the receptor in the same specific way that a substrate binds to the active site of an enzyme.
- The same equation and similar parameters are therefore used to describe the concentration-effect relationship.

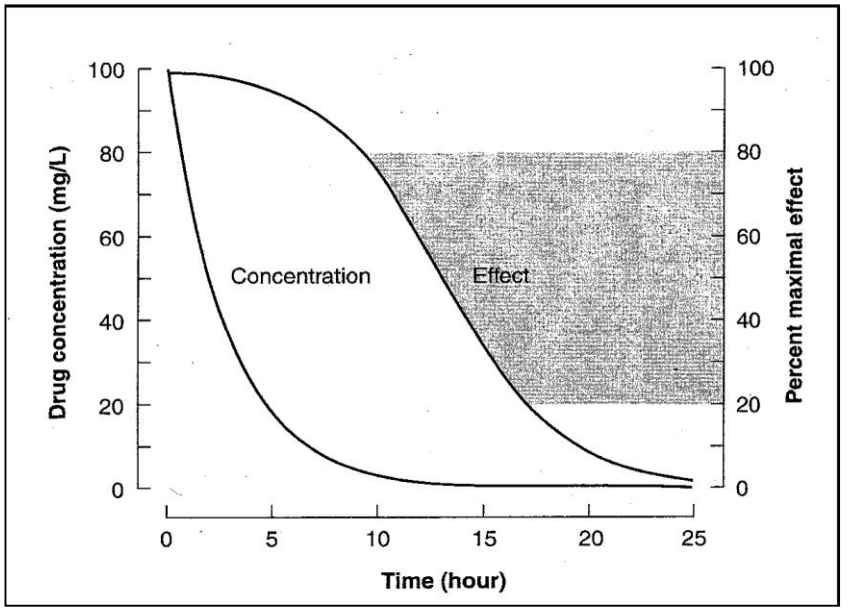




Drug concentration-effect relationship

Drug concentration-effect curve is linear between 20-80 %

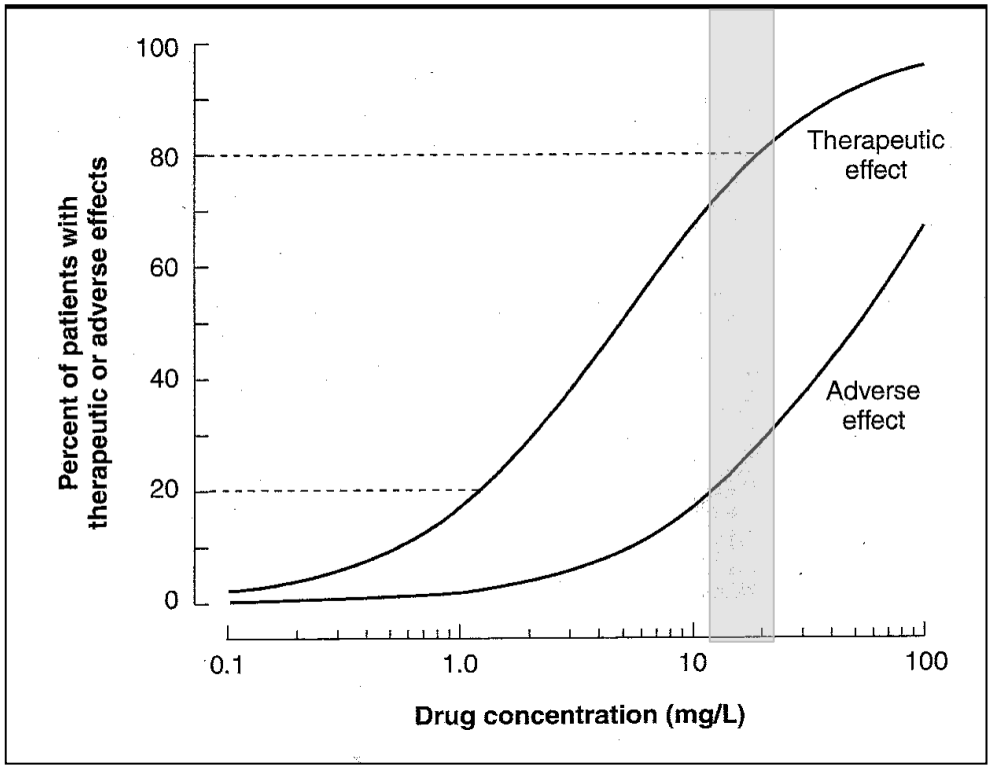




Drug effect after a single dose usually declines in a linear relationship with time in the range 20-80% maximal effect.

How is a therapeutic range (window) defined ?

- A therapeutic or target concentration range (therapeutic window) is the drug concentration range over which most patients will have a therapeutic effect with few having adverse effects.



Quantal (population) concentration-effect curves and the concept of the therapeutic range (window)

The therapeutical index

•The therapeutical index or therapeutical ratio is a comparison of the drug amount needed for a therapeutic action to the amount causing toxicity

•In animal studies:

Therapeutic index = $\frac{LD_{50}}{ED_{50}}$,

LD_{50} dose at which 50 % of the treated animals dies (Lethal Dose)

ED_{50} dose at which 50 % of the animals are cured (Effective Dose)

•In human studies:

Therapeutic index = $\frac{TD_{50}}{ED_{50}}$,

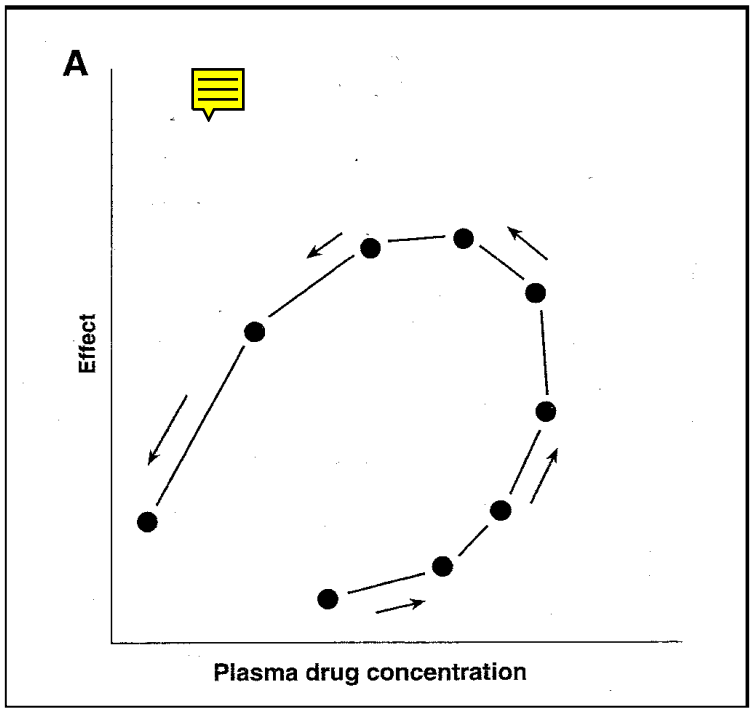
TD_{50} dose at which 50 % of the humans show poison related symthomes (Toxic Dose)

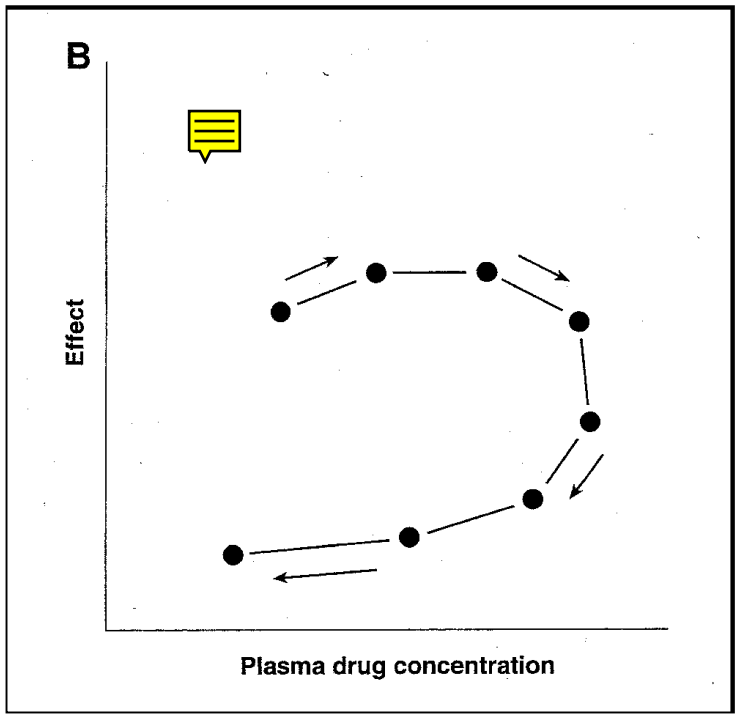
ED_{50} dose at which 50 % of the humans are cured (Effective Dose)

• Toxicity limiting in human studies

When is drug concentration not a good indicator of effect ?

Hysteresis in the concentration-effect relationship





When is drug concentration not a good indicator of effect ?

- A number of mechanisms results in dissociation of the usual relationship between drug concentration and effect.

- *Delayed distribution.*
- *Acute tolerance (tachyphylaxis).*
- *Drugs used at concentrations which give a maximal effect.*
- *'Hit and run' drugs.*
- *The 'wrong' effect is measured.*
- *Active metabolites.*
- *Enantiomeric drugs.*
- *Saturable protein binding.*

Questions ?

- ***With respect to graded conentration-effect curves :***

  a) E_{max} is the drug concentration at maximal effect
  b) EC_{50} is the drug concentration at half maximal effect
  c) when plotted as log concentration versus effect, the curve is approximately linear up to 50% of maximal effect
  d) a drug concentration twice EC_{50} gives an effect that is two-thirds E_{max}
  e) a drug concentration half EC_{50} gives an effect that is one-quarter E_{max}

- ***With respect to the time course of drug effect after a single dose :***

  a) effect falls in a linear fashion with time over the range 20%-80% of maximal effect
  b) above 80% maximal effect, the drug effect decreases rapidly as drug concentration decreases
  c) doubling the dose doubles the duration of action
  d) duration of action is a linear function of dose

- ***The therapeutic index :***

  a) is the ratio between the maximal therapeutic and toxic effects
  b) is the ratio between the EC_{50} for a toxic effect and the EC_{50} for the therapeutic effect
  c) depends on the potency of the drug
  d) is usually greater than 1
  e) refers to the potential to cause allergic drug reactions