

Pharmacokinetics II

By

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Pharmacokinetics (PK)

PK parameters :-

- ✓ Absorption
- ✓ Distribution
- ✓ Metabolism
- ✓ Elimination

- Two major routes involved in the process of drug elimination which are :-

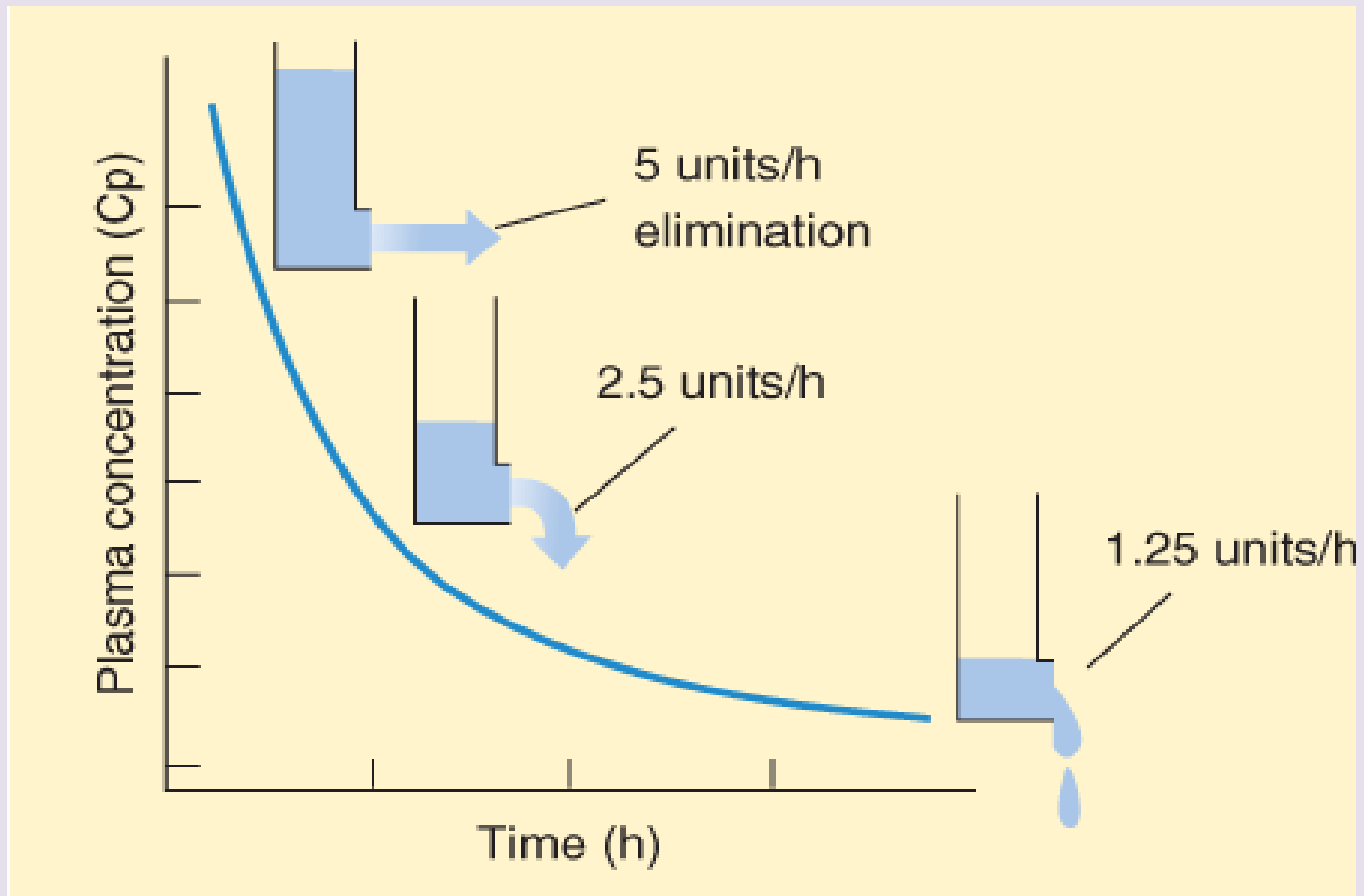
- 1) Metabolism.

- 2) Excretion in urine/ bile.

Clearance (CL)

- The volume of plasma cleared of the drug per unit time.
- $CL = 0.7 * V_d / t_{1/2}$.
- Clearance is an estimate for all processes of drug elimination from the body.

$$CL = \text{Rate of elimination} / C_p$$



- Clearance is constant in medically stable patients, **T** or F ?
- Rate of elimination decreases as C_p decreases, **T** or F ?

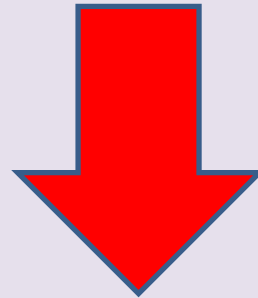
Metabolism

Kinetics of metabolism

A. 1st order kinetics

- A constant fraction of the drug present in the body is metabolized per unit of time.
- Most drugs follow 1st order kinetics.
- 1st order kinetics also called linear / exponential kinetics .

$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$

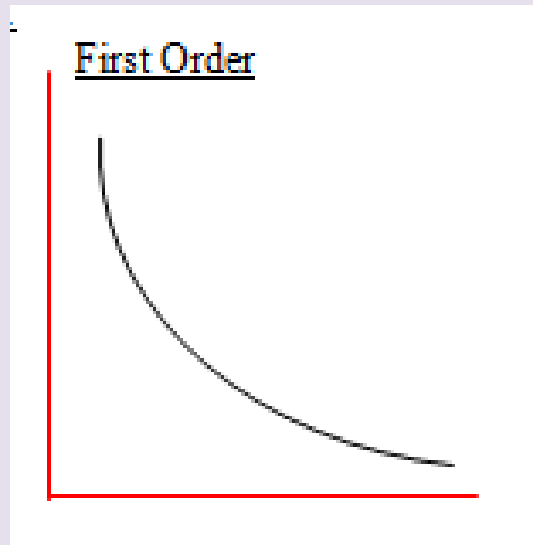


$$[C] \ll K_m$$

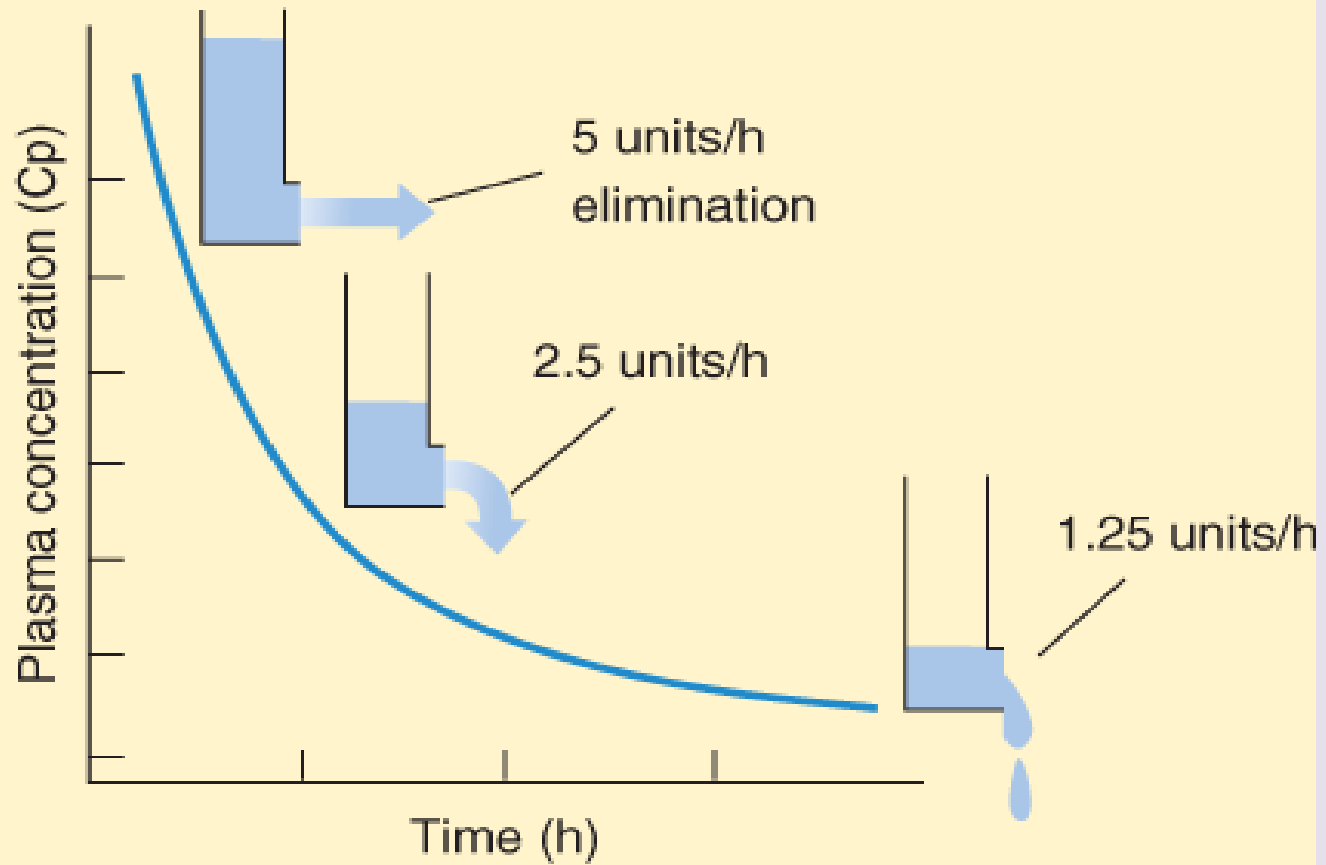
$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m}$$

- ✓ The rate of drug metabolism is directly proportional to the concentration of free drug .

Concentration



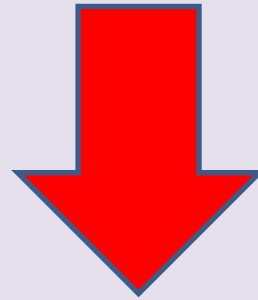
Time



B. Zero-order kinetics

- Only few drugs follow zero order kinetics such as aspirin , ethanol and phenytoin.
- The rate of metabolism of these drugs (v) is very high , what about K_m of the reaction ?

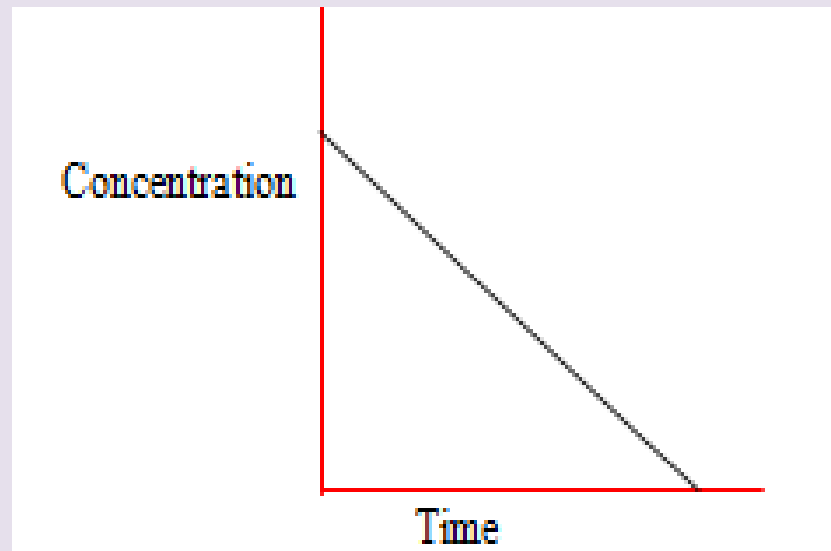
$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{K_m + [C]}$$



$$K_m \ll [C]$$

$$v = \text{rate of drug metabolism} = \frac{V_{\max} [C]}{[C]} = V_{\max}$$

✓ The rate of drug metabolism is constant.



Reactions of drug metabolism

- Why does the body need to metabolize drugs?
- The process of drugs (xenobiotics) metabolism involves two phases :-

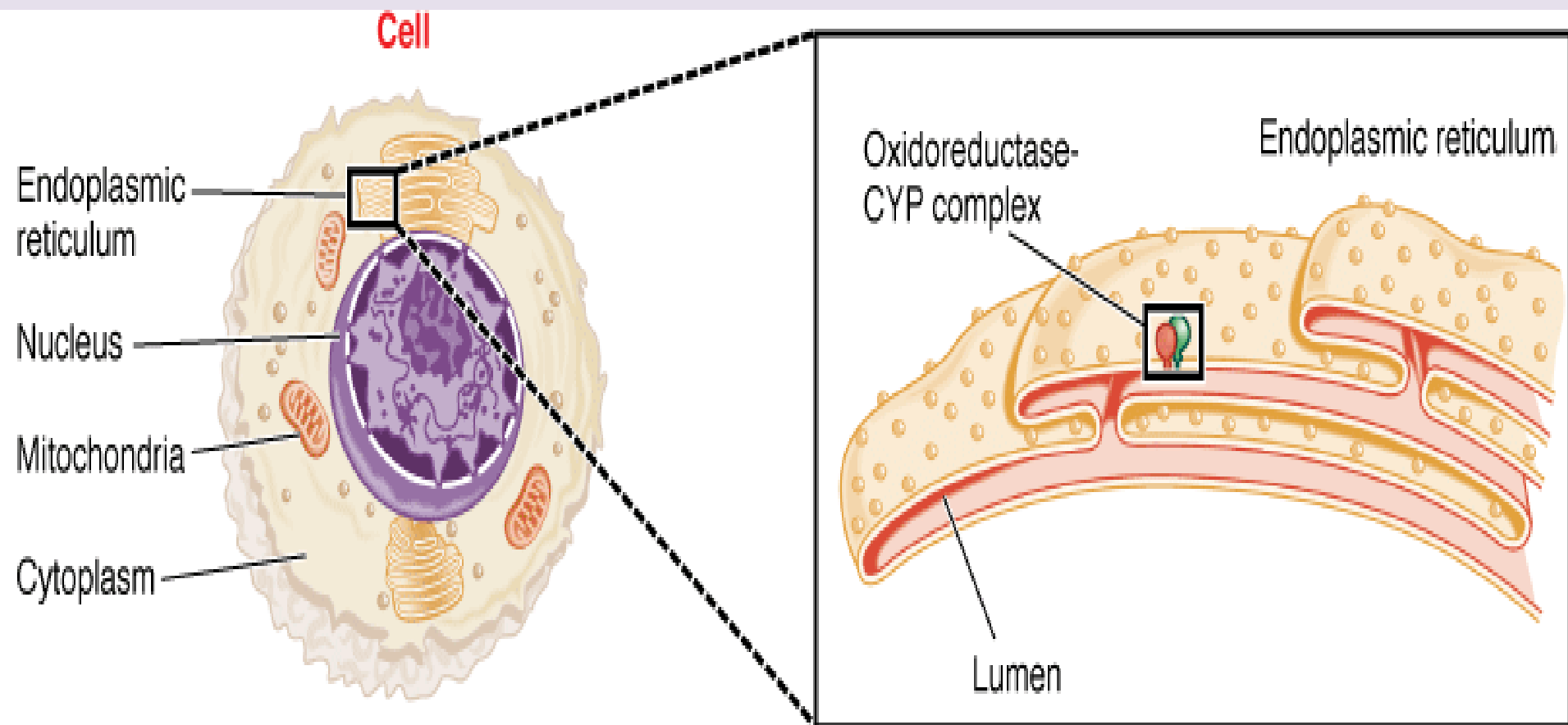
Phase I reactions

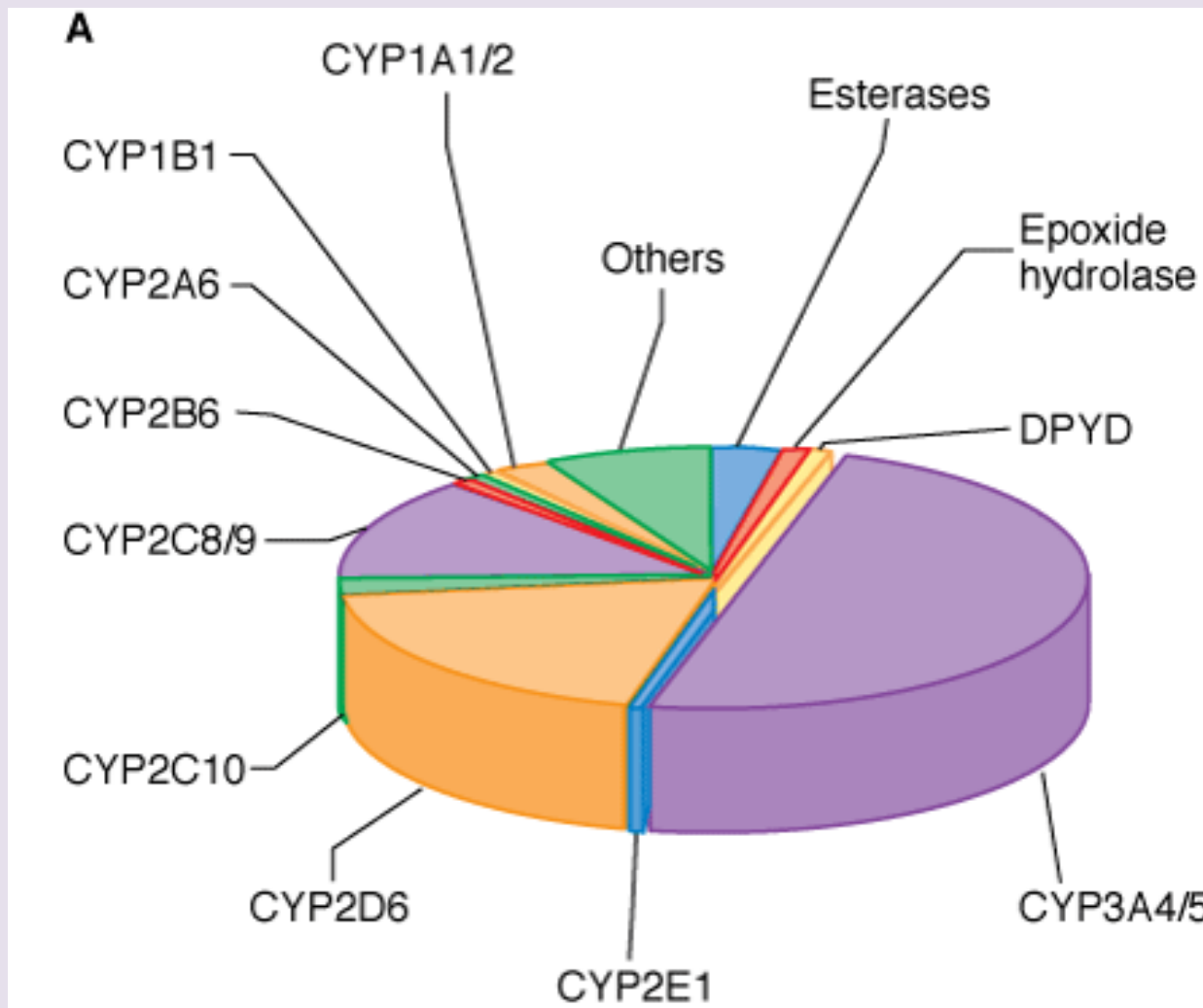
- Phase I reactions convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group.
- Oxidation reactions are mostly cytochrome P450-dependent.

Reaction Type
Oxidations, P450 dependent
Hydroxylation
<i>N</i> -dealkylation
<i>O</i> -dealkylation
<i>N</i> -oxidation
<i>S</i> -oxidation
Deamination
Oxidations, P450 independent
Amine oxidation
Dehydrogenation
Reductions
Hydrolyses
Esters
Amides

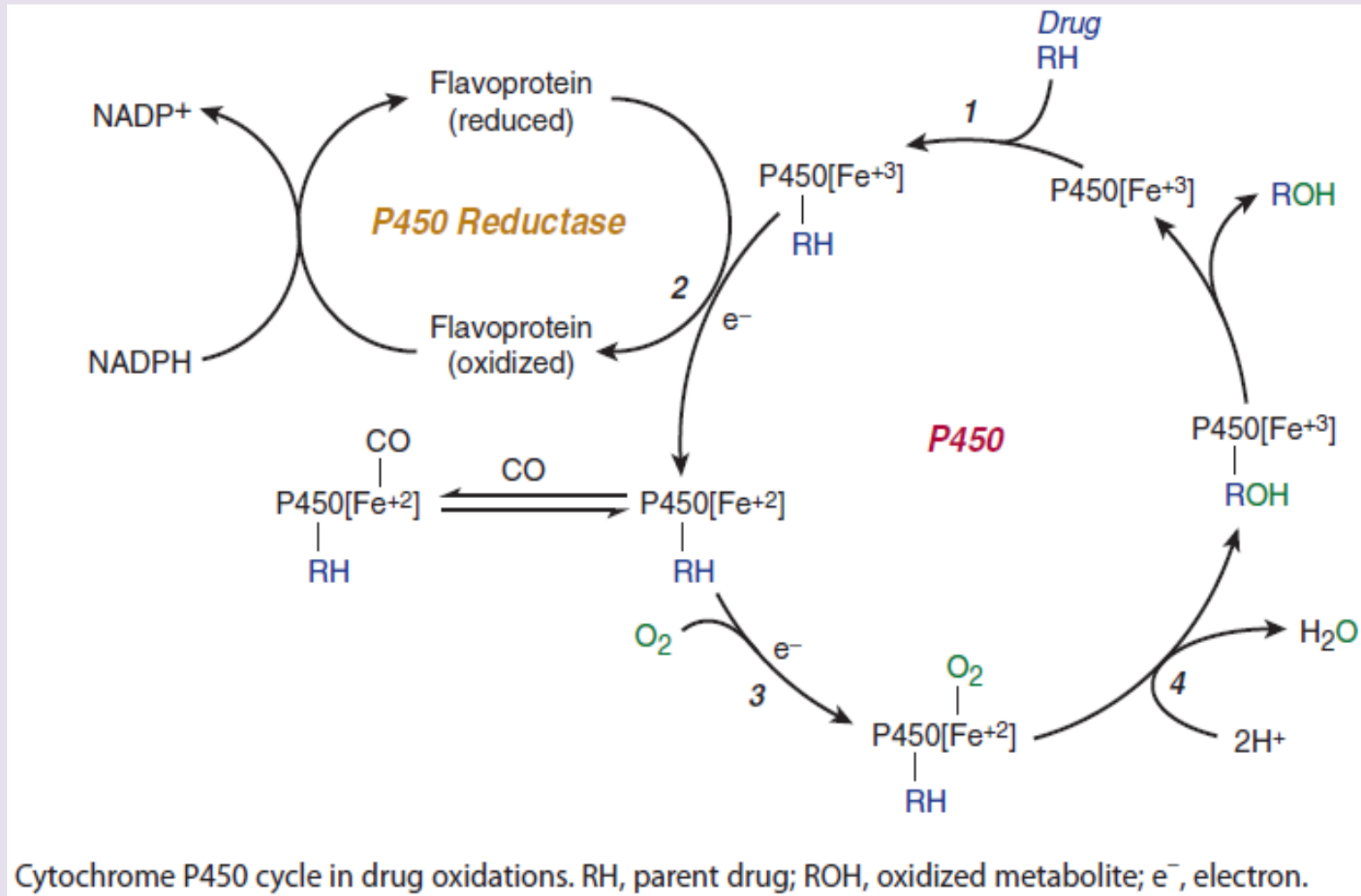
Cytochrome-P450

- is a hemoprotein that catalyzes many of the oxidation reactions in hepatocytes and other cells.
- Exhibits low selectivity for its substrates.
- Many isoforms of this enzyme are present.





Of the drugs metabolized by phase I cytochrome P450s, approximately 75% are metabolized by just two: CYP3A4/5 or CYP2D6



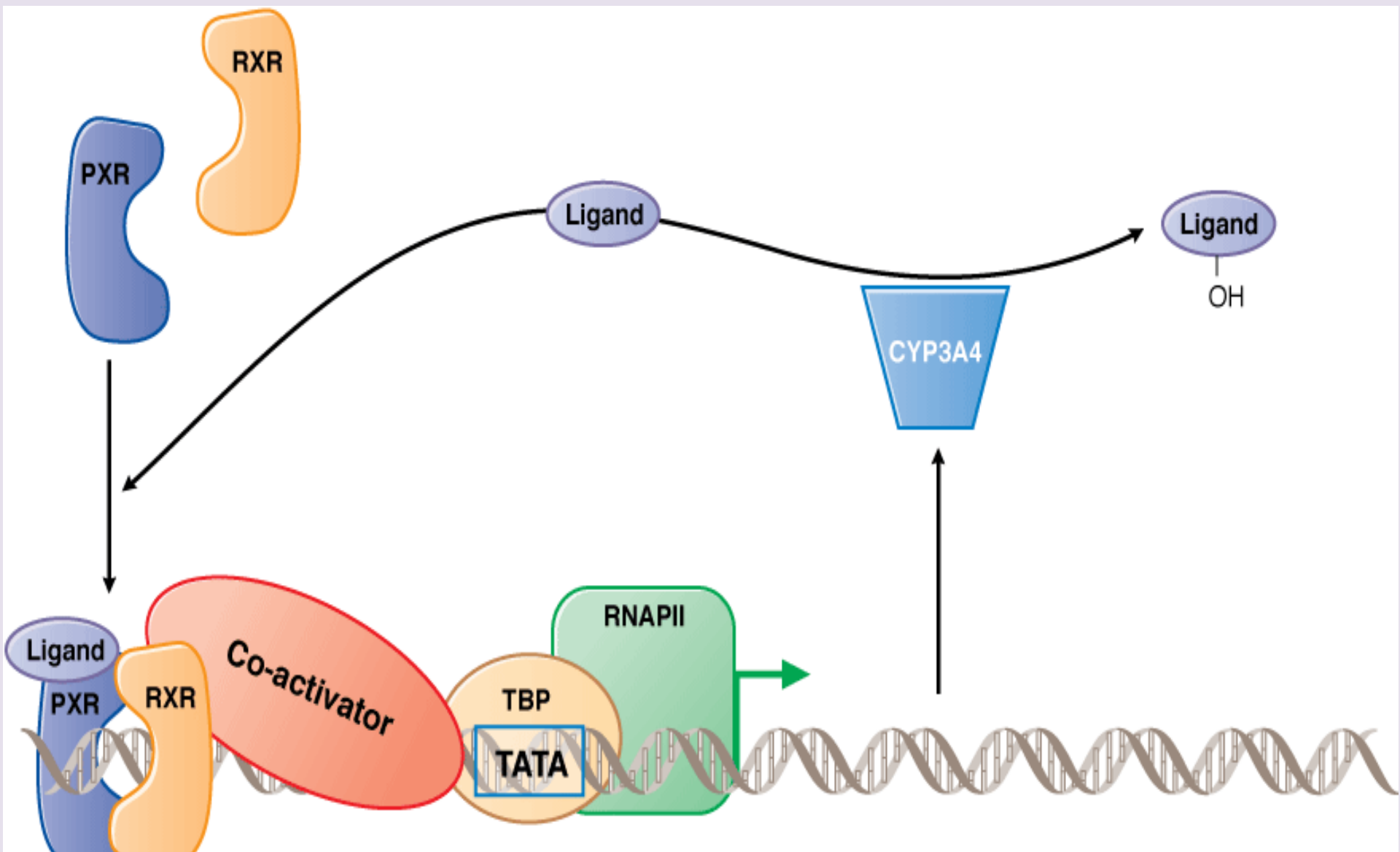
What is the effect of Phase I metabolism on drug's pharmacological activity ?

Answer

Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity.

Enzyme induction/ inhibition

- Xenobiotics can induce the activity of cytochrome P450 isozymes by inducing the expression of the genes encoding the enzyme or by stabilizing the enzyme itself.
- Xenobiotic usually inhibit metabolic enzymes through competition.



- Examples of enzyme inducers : Benzo α -pyrene (from tobacco) , carbamazepine , rifampin , barbiturates (esp. phenobarbital) and phenytoin.
- Examples of enzyme inhibitors : Cimetidine , macrolides (e.g. erythromycin), grapefruit juice , metronidazole , omeprazole and chloramphenicol.

Drug-Drug interaction through enzyme induction/inhibition

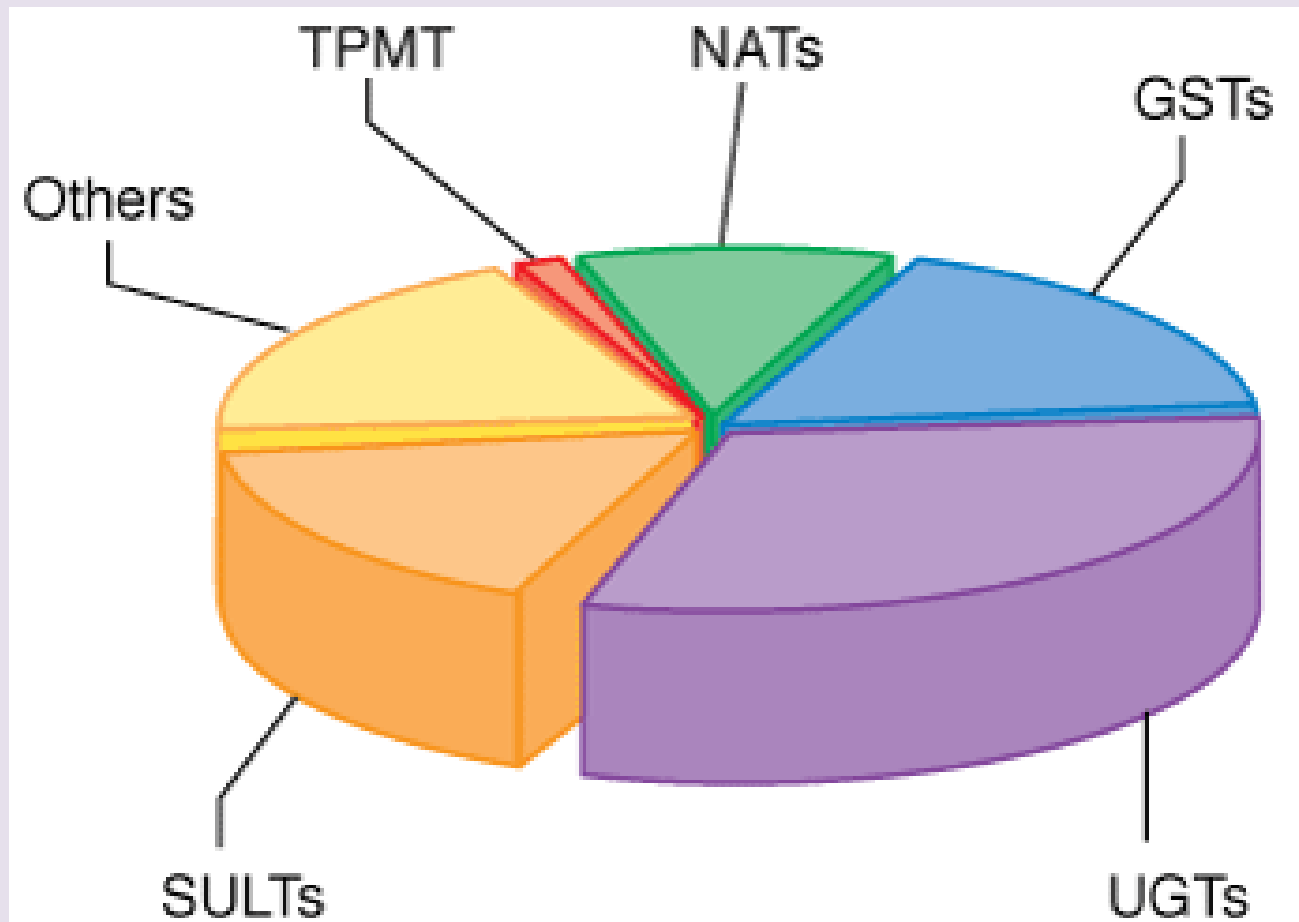
- Example 1: Omeprazole and warfarin.
- Example 2: Benzo α -pyrene and theophylline.

Phase II reactions

- This phase consists of conjugation reactions to in order to increase drug polarity.
- Conjugation reactions generally inactivate the drug being metabolized (except morphine).

Conjugation reactions

Reaction Type
Glucuronidation
Acetylation
Glutathione conjugation
Glycine conjugation
Sulfation
Methylation



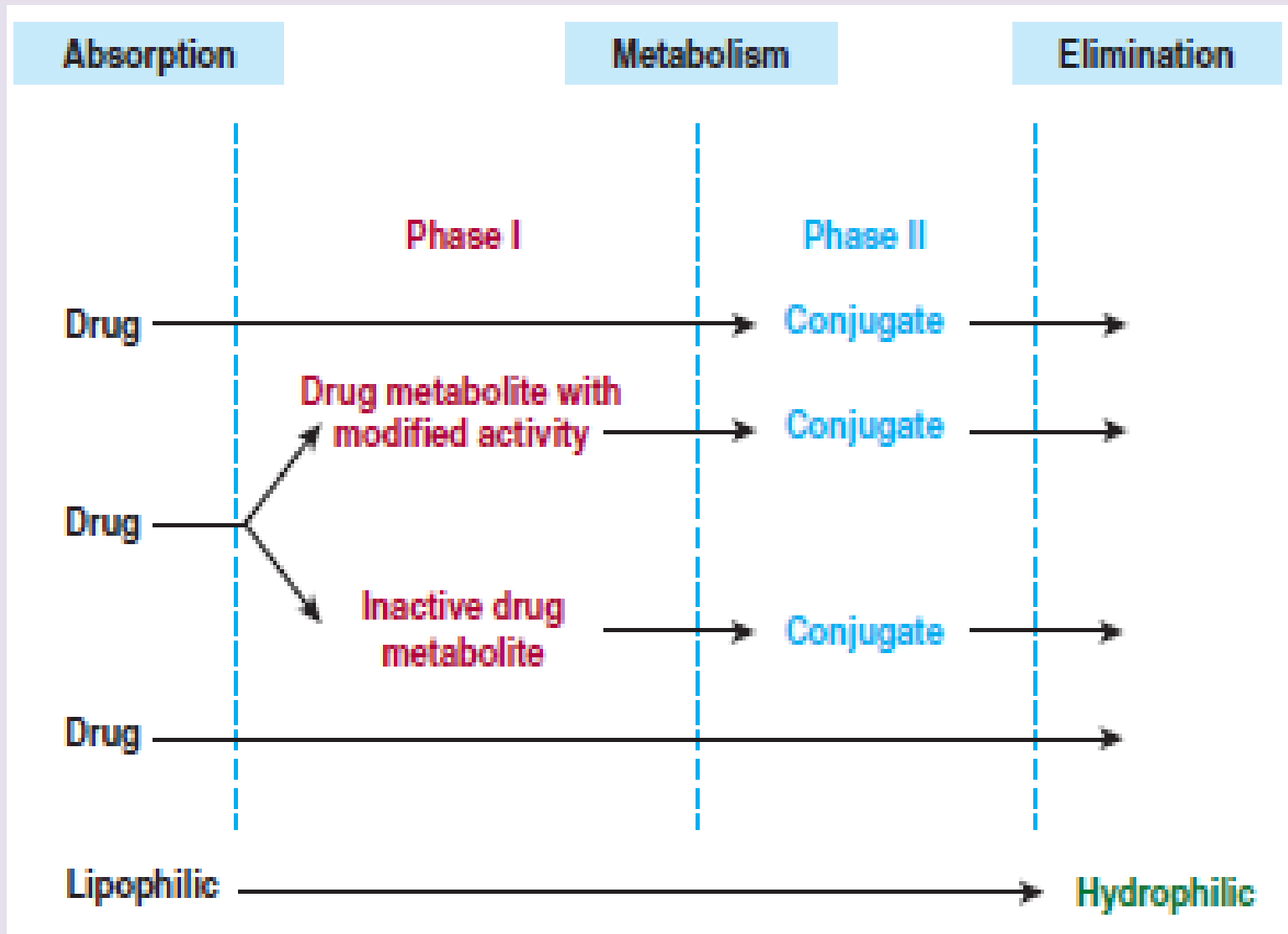
UGT : UDP-glucuronosyl transferase.

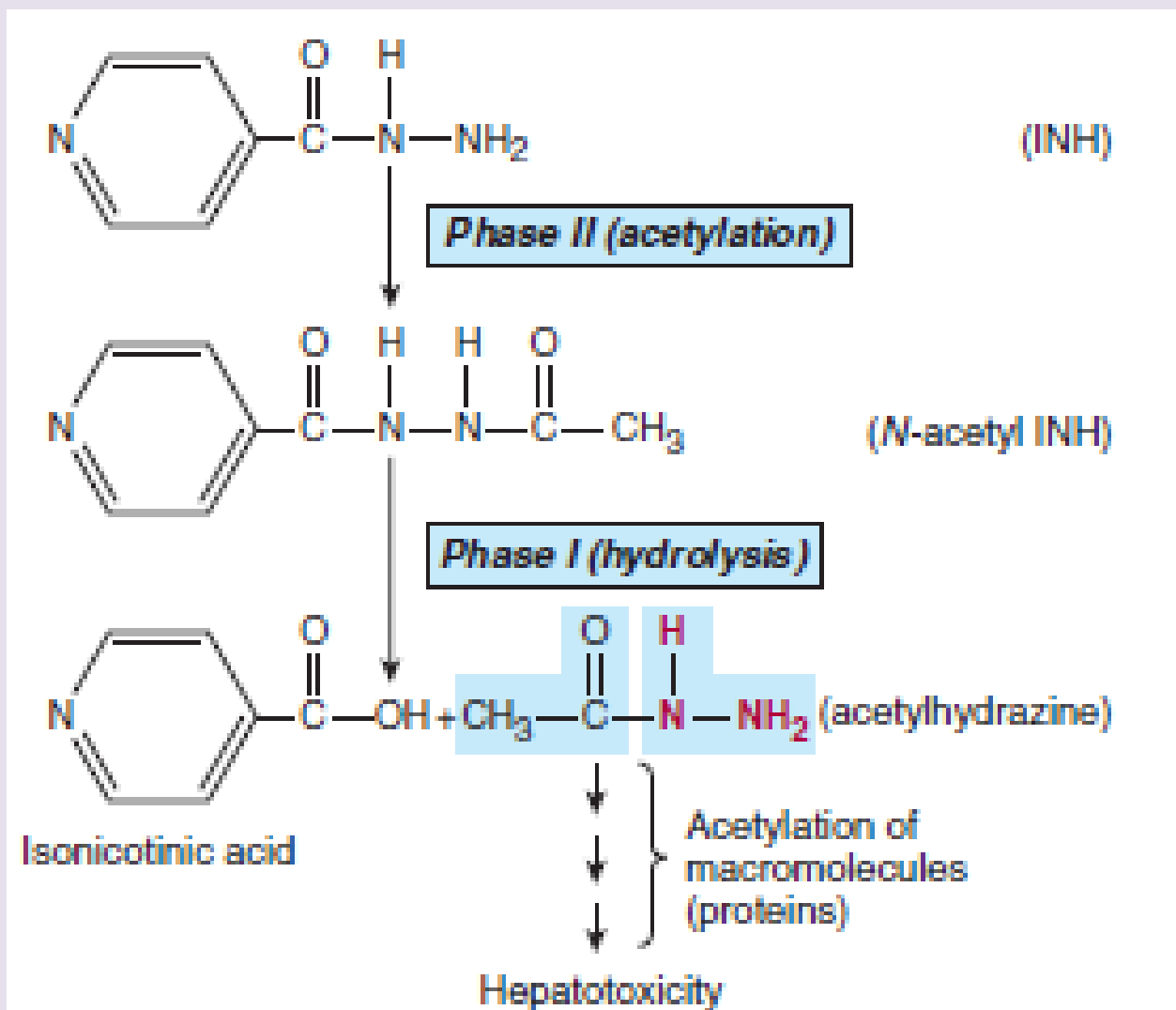
GST : glutathione- *S* –transferase.

SULT : sulfotransferase.

NAT : N-acetyl transferase.

Order of metabolic reactions

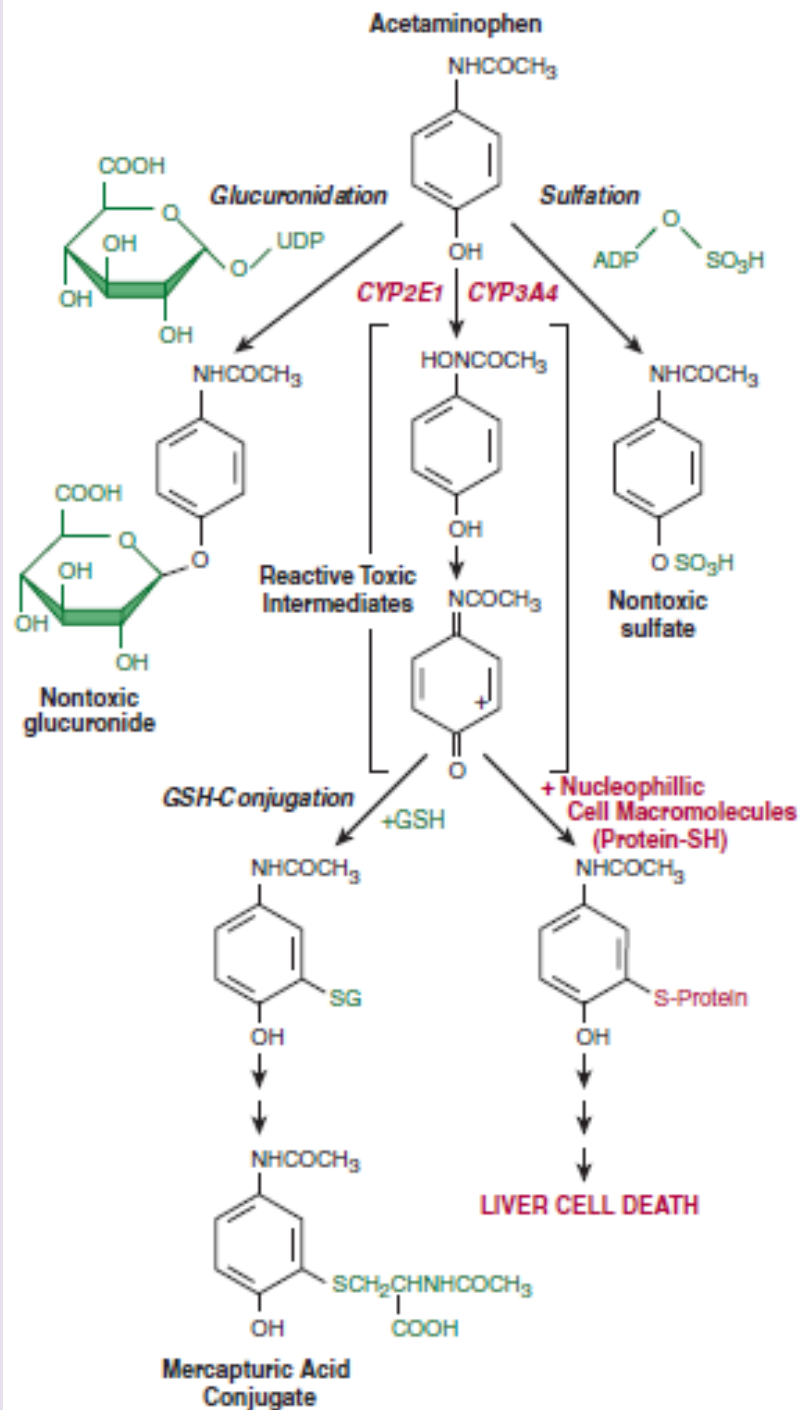




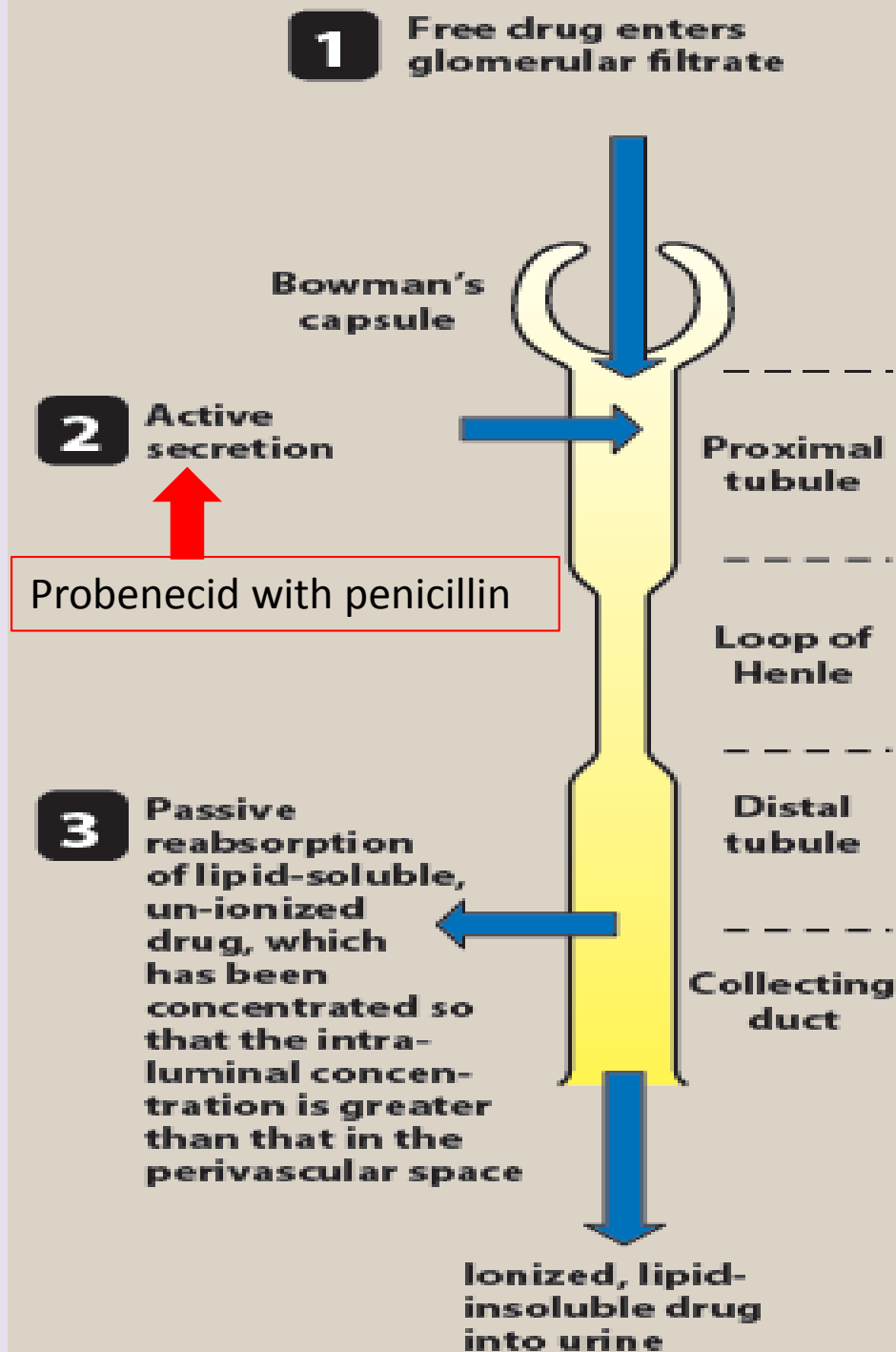
Pharmacogenetics

- Refers to genetic differences in metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.
- **Example 1:** Poor CYP2C19 metabolizers using clopidogrel.
- **Example 2:** Defective conjugation system in neonate (chloramphenicol).

Toxic metabolism



Elimination by kidney



Clearance via other routes

- Bile.
 - Lungs.
 - Milk in nursing mothers.
 - Sweat, saliva, tears, hair, and skin.
-
- $CL_{\text{total}} = CL_{\text{hepatic}} + CL_{\text{renal}} + CL_{\text{pulmonary}} + CL_{\text{other}}$

Clinical situations affecting $t_{1/2}$

Clinical situations that can increase $t_{1/2}$:-

1. Decreased renal/hepatic blood flow (cardiogenic shock , heart failure & haemorrhage).
2. Renal/hepatic diseases (renal insufficiency , cirrhosis).

Clinical situations that can decrease $t_{1/2}$:-

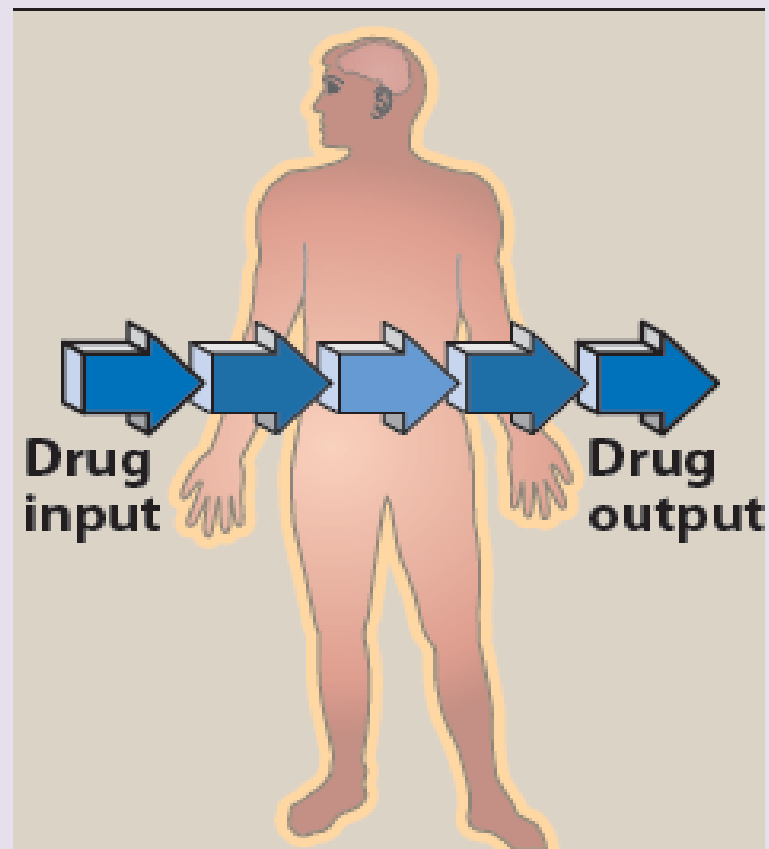
1. Decrease plasma protein binding (liver disease , nephrotic syndrome).
2. Increased metabolic rate (enzyme induction).
3. Increased hepatic blood flow.

Optimization of dosage regimen

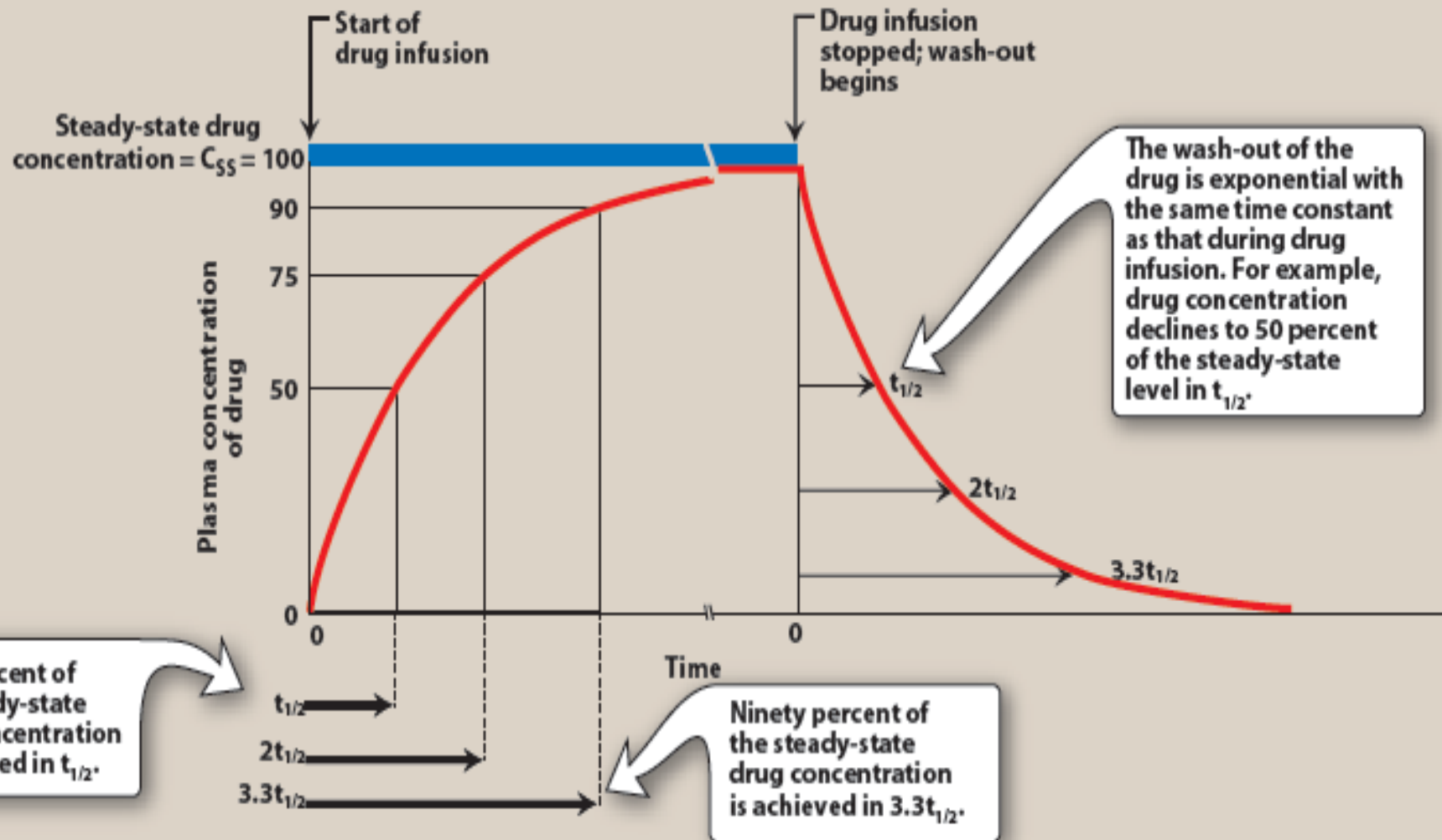
What is steady state (ss) ?

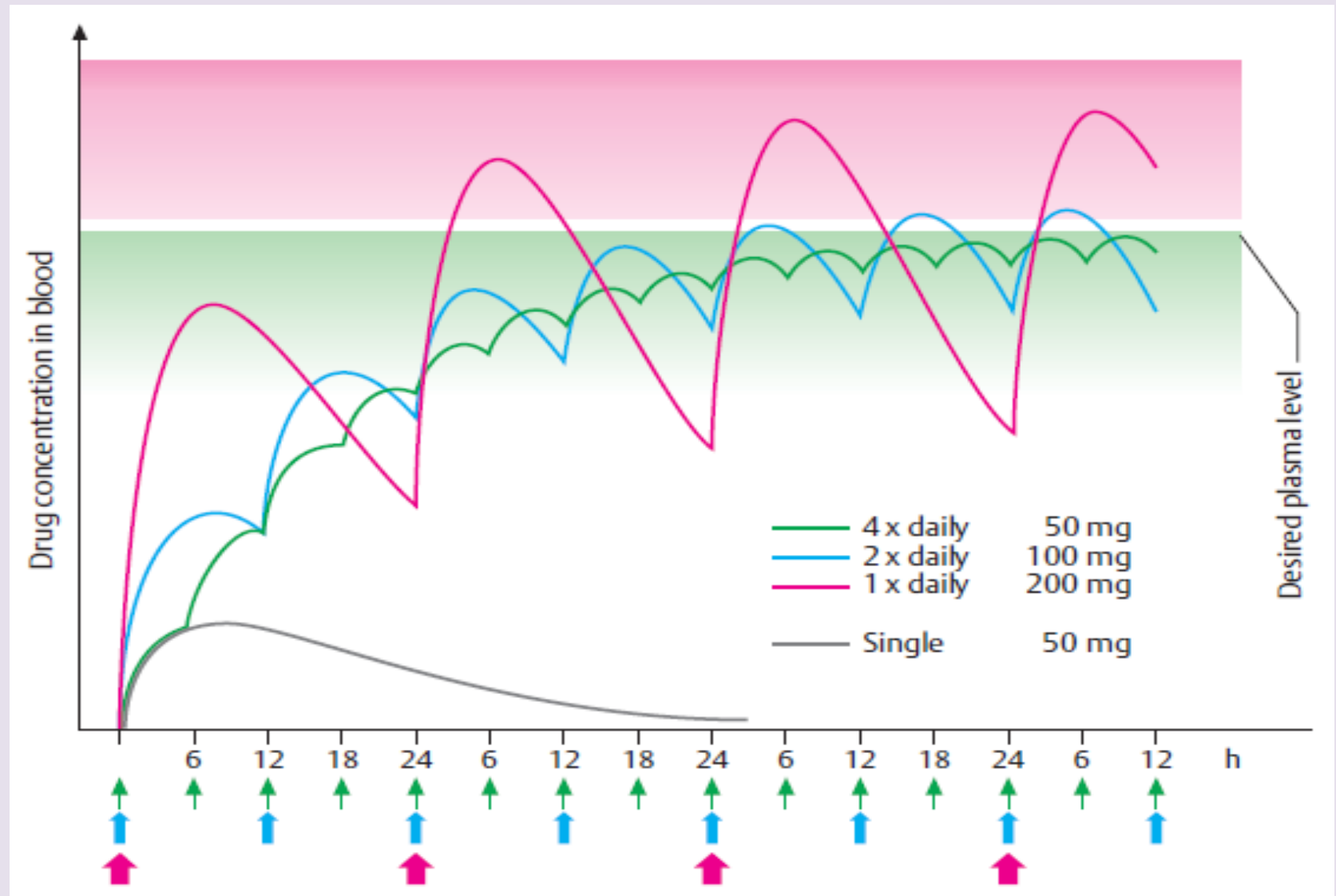
❑ It's the point at which the amount of drug administered is equal to the amount being eliminated.

❑ Plasma/tissue levels remain constant in case of IV infusion or fluctuate around a mean in oral/IV fixed dose regimens.



Time to reach steady state





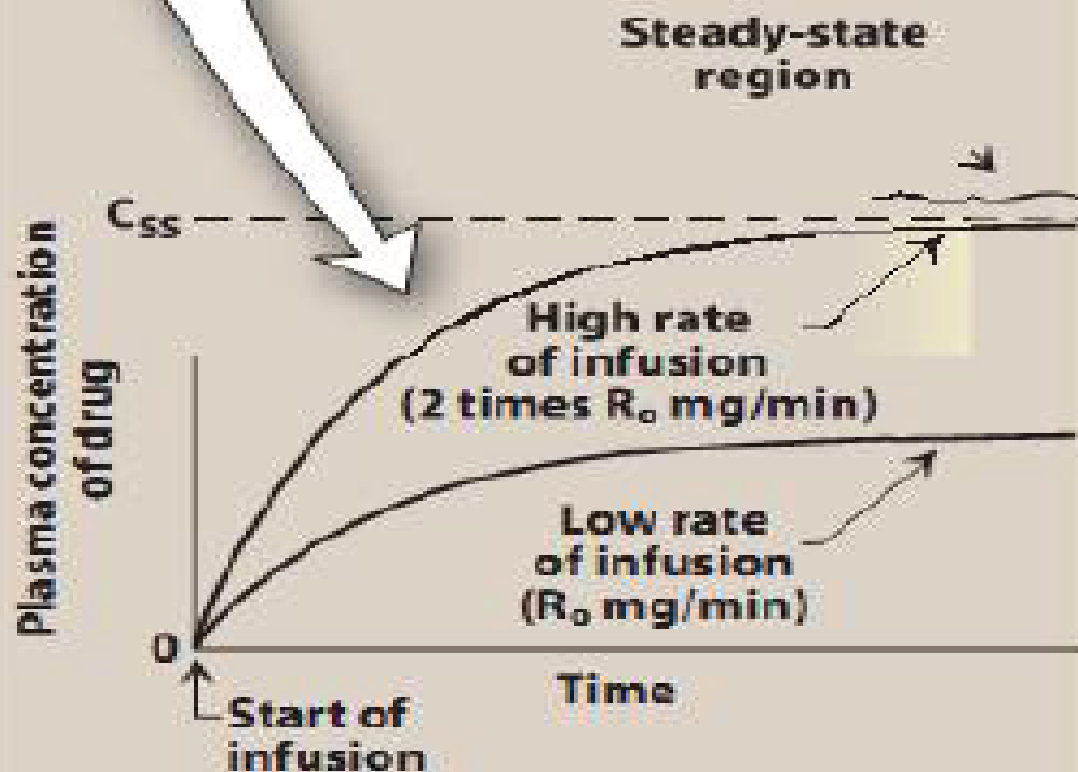
A. Continuous IV-infusion regimens

- Rate of drug input is constant .
- Rate of drug elimination increases as C_p increases , why ?

What is the effect of infusion rate on:

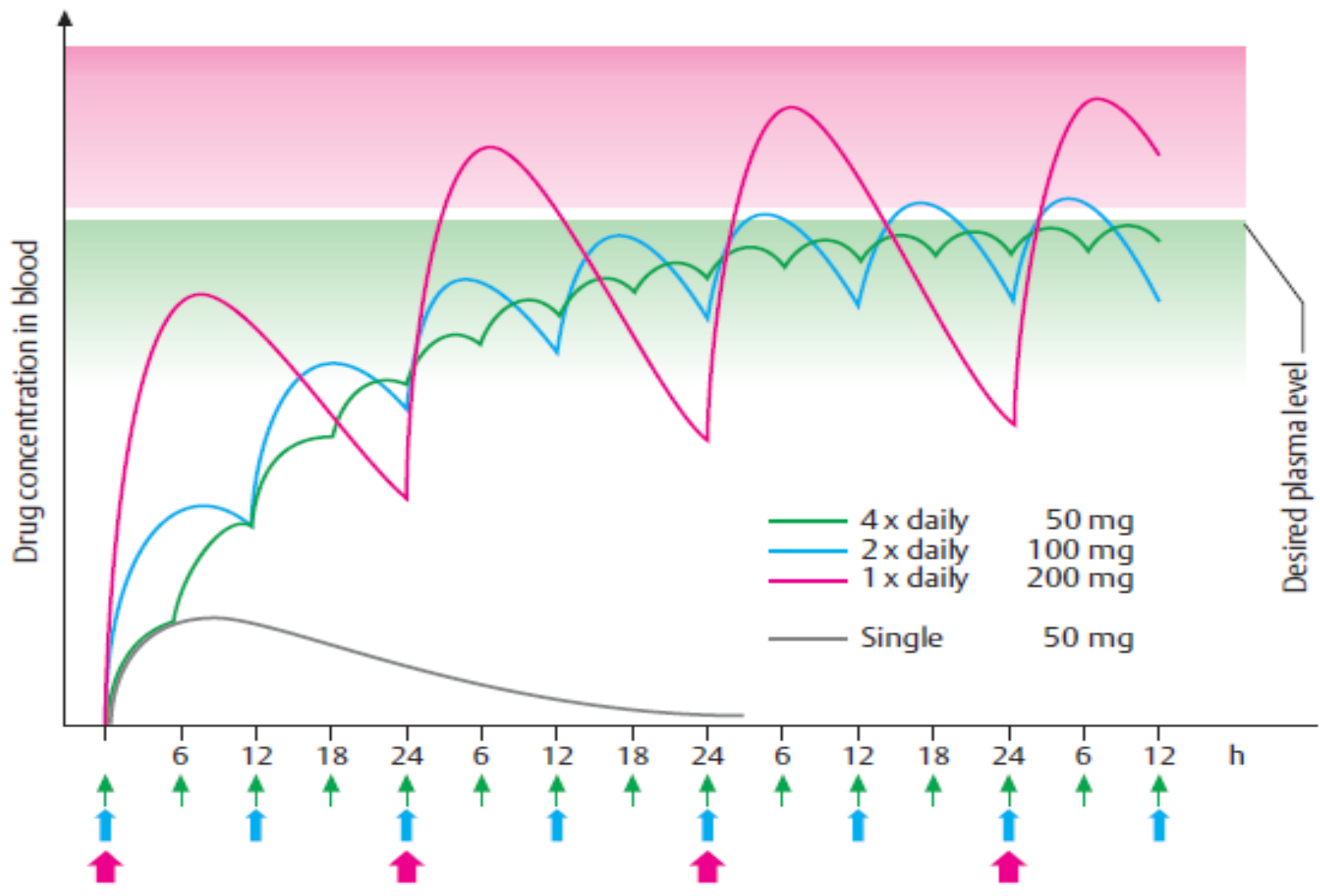
1. Time needed to reach steady state ?
2. Steady state concentration ?

Note: A faster rate of infusion does not change the time needed to achieve steady state. Only the steady-state concentration changes.



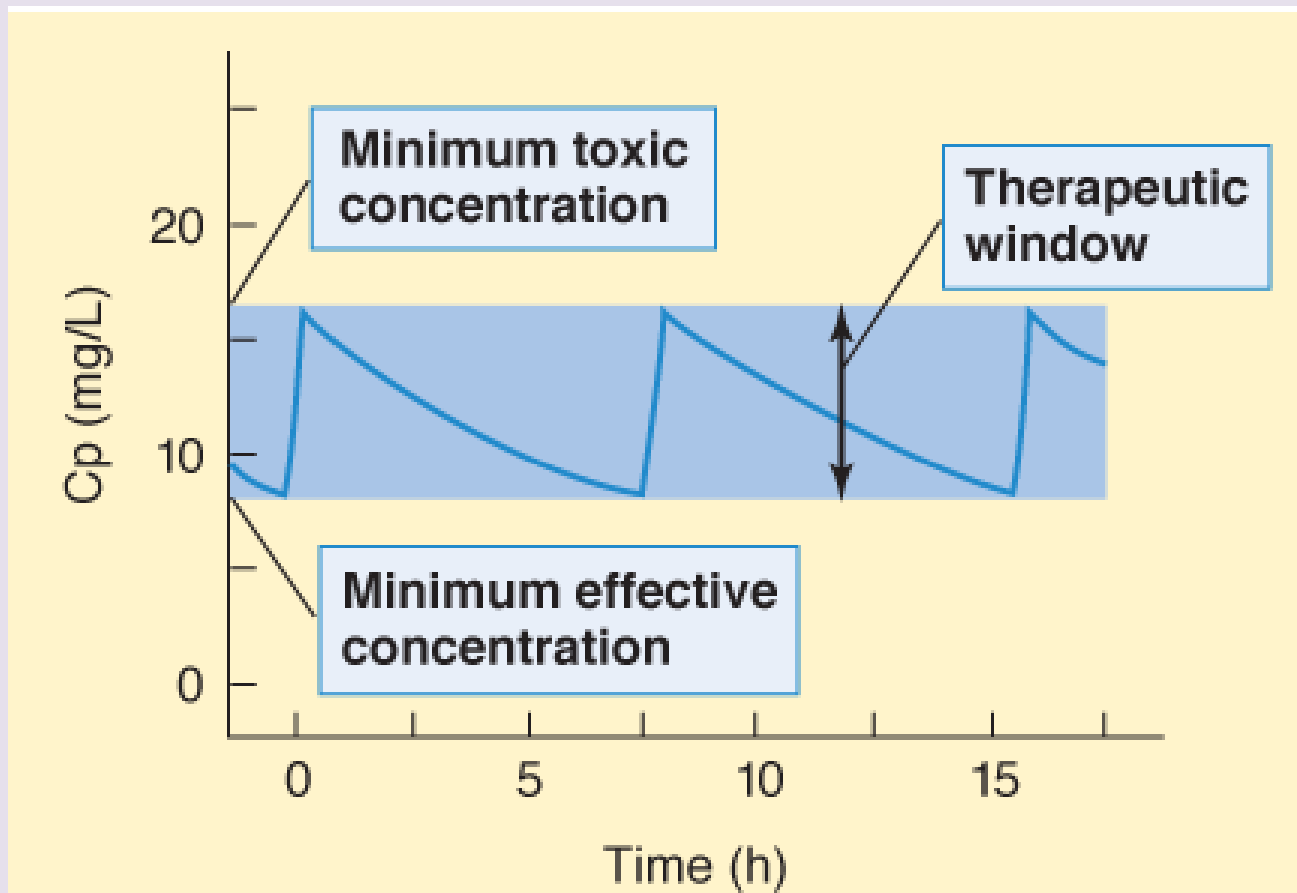
B. Fixed-dose/fixed-time regimens

- Does dosing frequency affect the steady-state concentration of the drug, and the rate at which the steady state is approached ?
- Using smaller doses at shorter intervals reduces the amplitude of the swings in drug concentration.



1. Maintenance of dose

- Drugs are generally administered to maintain a steady-state concentration within the therapeutic window.



Maintenance dose = (Dosing rate/F) * Dosing interval

$$\text{Dosing Rate} = \frac{(\text{target } C_{\text{plasma}})(\text{CL})}{F}$$

Example

A target plasma theophylline concentration of 10 mg/L is desired to relieve acute bronchial asthma in a 70-kg patient. The patient is a nonsmoker and otherwise normal except for asthma, drug clearance is estimated to be 2.8 L/h/70 kg. Calculate the proper infusion rate to reach the desired plasma conc. ?

$$\begin{aligned}\text{Dosing rate} &= \text{Target } C_p \times \text{CL} / F \\ &= 10 \text{ mg/L} \times 2.8 \text{ L/h} \\ &= 28 \text{ mg/h.}\end{aligned}$$

Therefore, in this patient, the proper infusion rate would be 28 mg/h.

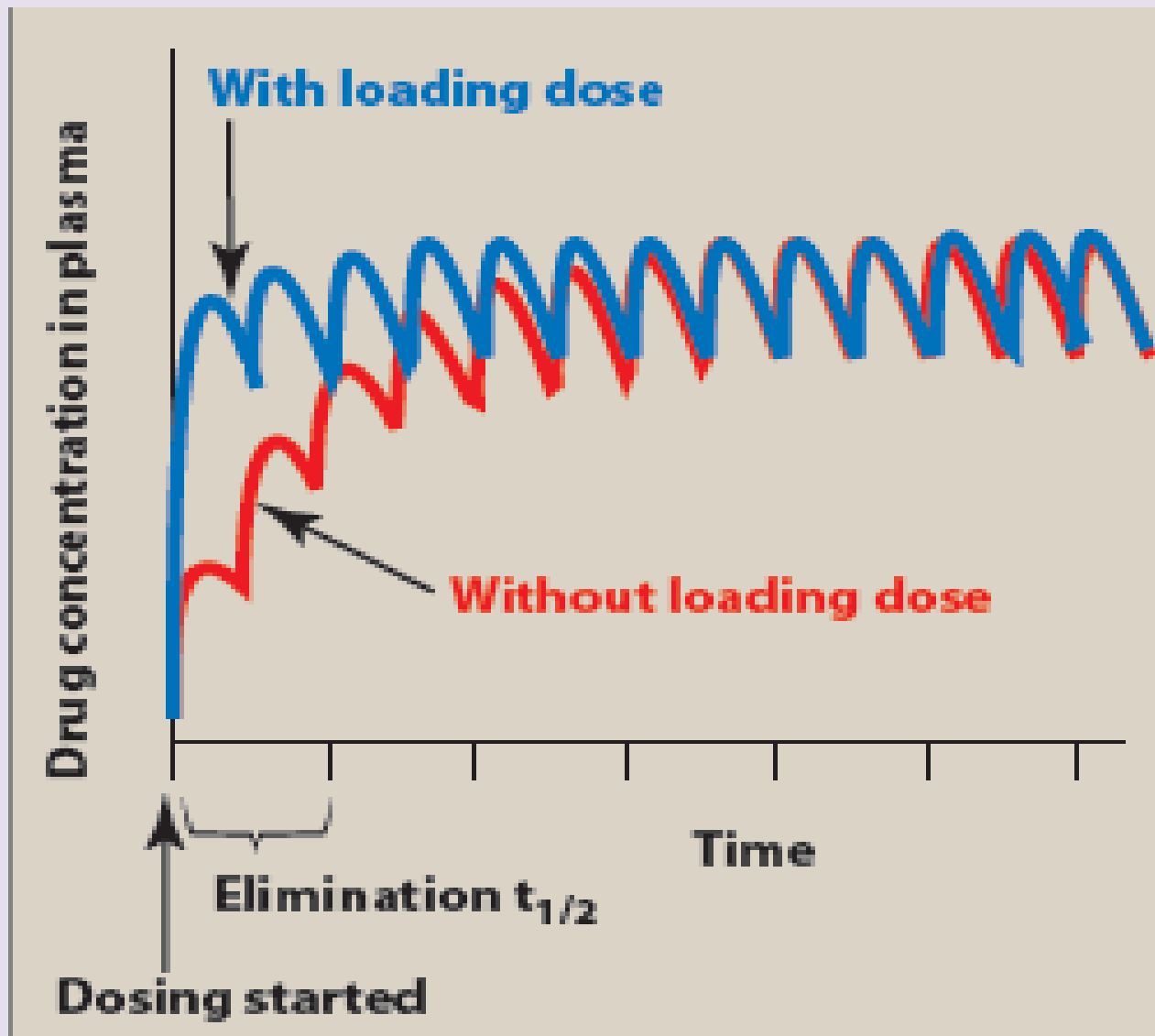
If the asthma attack is relieved, the clinician might want to maintain this plasma level using oral theophylline ($F=0.96$), which might be given every 12 hours using an extended-release formulation. Calculate the proper oral maintenance dose ?

$$\begin{aligned}\text{Maintenance dose} &= (\text{Dosing rate} / F) \times \text{Dosing interval} \\ &= (28 \text{ mg/h} / 0.96) \times 12 \text{ hours} \\ &= 350 \text{ mg}\end{aligned}$$

A tablet or capsule size close to the ideal dose of 350 mg would then be prescribed at 12-hourly intervals. If an 8-hour dosing interval was used, the ideal dose would be 233 mg; and if the drug was given once a day, the dose would be 700 mg.

2. Loading dose

- A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a “loading dose” of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose).
- Loading dose = $C_p \times V_d / F$
- Does the use of loading dose decrease the time needed to reach ss ?



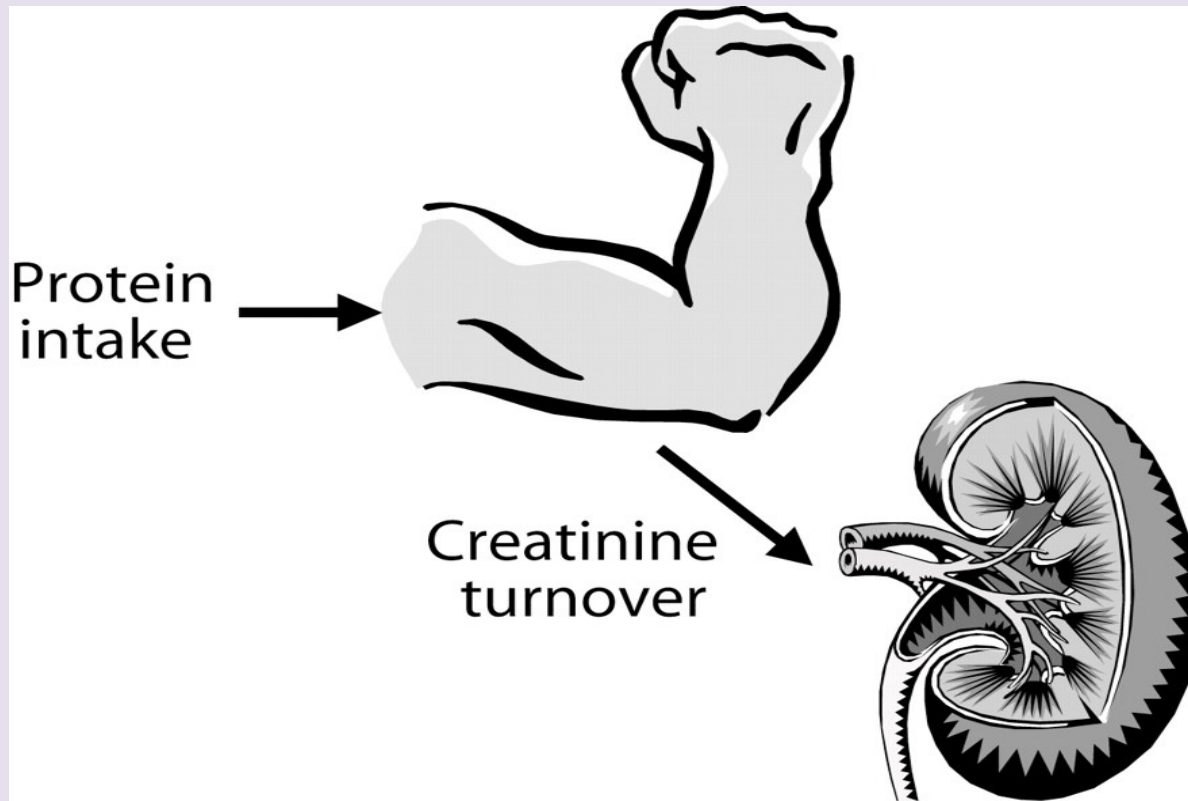
Example

- A patient was admitted to ER with severe CHF. The clinical decision was made to give IV digoxin with a target plasma conc. of 0.9 ng/ml. If V_d of digoxin is known to be 496 L, What's the loading dose required to obtain the desired C_p ?
- Loading dose = $C_p \times V_d / F$
= 0.9 ng/ml x 496 L
= 0.625 mg

Dose adjustment

Corrected dosage = average dosage $CL_{\text{creatinine}} / 100$.

- $CL_{\text{creatinine}} = (140 - \text{age}) * \text{Weight} / 72 * S_{\text{creatinine}}$
(multiply by 0.85 for females).



References

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