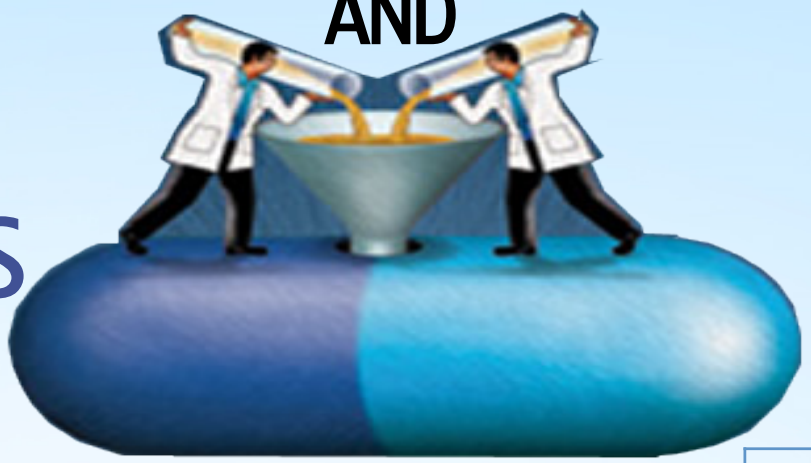
PHARMACOLOGY
433

King Saud University
College of Medicine
Foundation Block

Pharmacokinetics IV ; Drug Excretion

4

OBJECTIVES AND KEY WORDS



- Identify main and minor routes of Excretion including renal elimination and biliary excretion.
- Describe enterohepatic circulation and its consequences on duration of drugs.
- Describe some pharmacokinetics terms including clearance of drugs.
- Biological half-life (t ½), multiple dosing, steady state levels, maintenance dose and Loading dose.

Renal Excretion
Biliary Excretion
Glomerular filtration(GFR)
Passive tubular reabsorption
Active tubular secretion
Urinary pH trapping
Enterohepatic circulation
Plasma half-life (t ½)
Loading and Maintenance dose

Routes of Excretion

Major :

A) Renal Excretion
By the Kidney

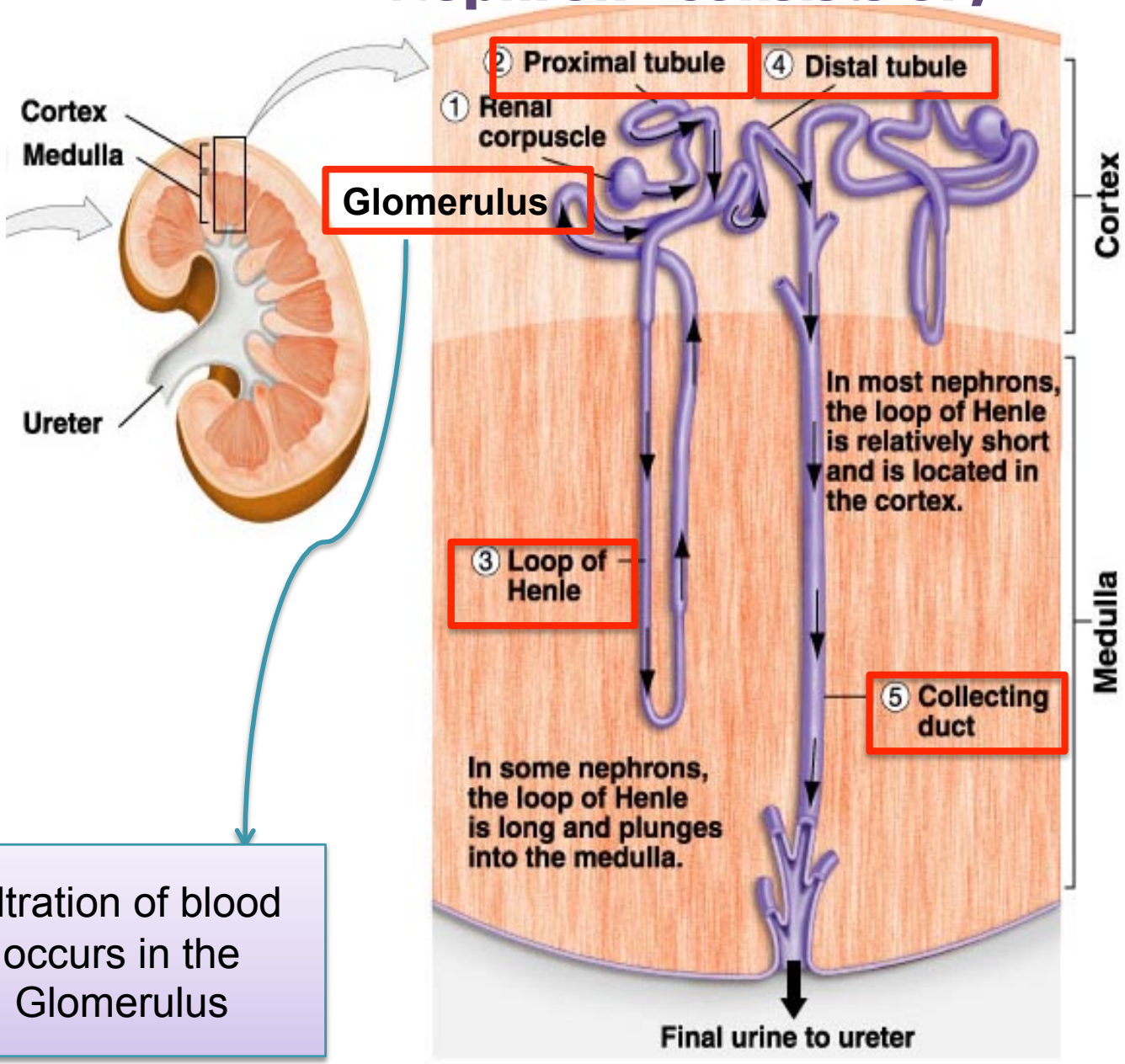
B) Biliary Excretion
By the liver

Minor :

* Exhaled air (exhalation)
* Salivary
* Sweat
* Milk "in Breast-feeding women"
* Tears

Structure of the Kidney

"Nephron" consists of ;



Filtration of blood occurs in the Glomerulus

RENAL EXCRETION

Glomerular filtration. | Passive Tubular Re-absorption. | Active tubular secretion.

- **Depends upon renal blood flow (600 ml/ min)** "more blood flow, more filtration"

GFR* 20% of renal blood flow = 125 ml/min.

Glomerular filtration occurs to

- **Low MW drugs**
- **Free drugs (unbound to plasma proteins)**

If there is **Proteinuria** "protein in urine" in a urine sample, this means there's a **Glomerular disease**, because it let protein-bound drugs pass through it, which is abnormal.

	Distal Convoluted Tubules & Collecting Ducts	Mainly in Proximal Tubules
Location		
Function	-Passive diffusion of unionized, lipophilic drugs. -Lipophilic drugs can be reabsorbed back into blood circulation, and excretion in urine will be low. -Ionized drugs are poorly reabsorbed and so urinary excretion will be high.	Increases drug concentration in Lumen of tubules. "because of the secretion". Organic anionic(-) and cationic(+) transporters mediate active secretion of anionic and cationic drugs. Transport drugs against concentration gradients. "same characteristics as active transport in drug Absorption"

Penicillin "transport of acidic drugs is blocked by **probenecid**" — **Acidic drug.**

Morphine — **Basic drug.**

*Glomerular Filtration Rate

Urinary pH trapping (Ion trapping)

When does it happen ?

Changing pH of urine by chemicals can **inhibit or enhance** the tubular drug re-absorption back into blood.

Why does it happen ?

Ion trapping is used to **enhance** renal clearance of drugs during toxicity.

Remember that ..

Urine is normally slightly acidic, pH range : 4.6-8
Acidic drugs are best absorbed in acidic medium and best excreted in basic medium, while basic drugs are best excreted in acidic medium.

Alkaline means basic

Acidification and Alkalization

Acidification of urine using Ammonium Chloride (NH4Cl) **increases excretion of basic** drugs as Amphetamine.

Alkalization of urine using Sodium Bicarbonate $NaHCO_3$ **increases excretion of acidic** drugs as Aspirin.

Drugs excreted mainly by the kidney include:

-Aminoglycosides antibiotics (as gentamycin)
-Penicillin
-Lithium

These drugs should be prescribed carefully to:

-Patients with renal diseases. "because their renal excretion would be abnormal"

-Elderly people. "some might have renal dysfunction"

B) Biliary Excretion

By the liver

-Occurs to few drugs that are excreted into feces.

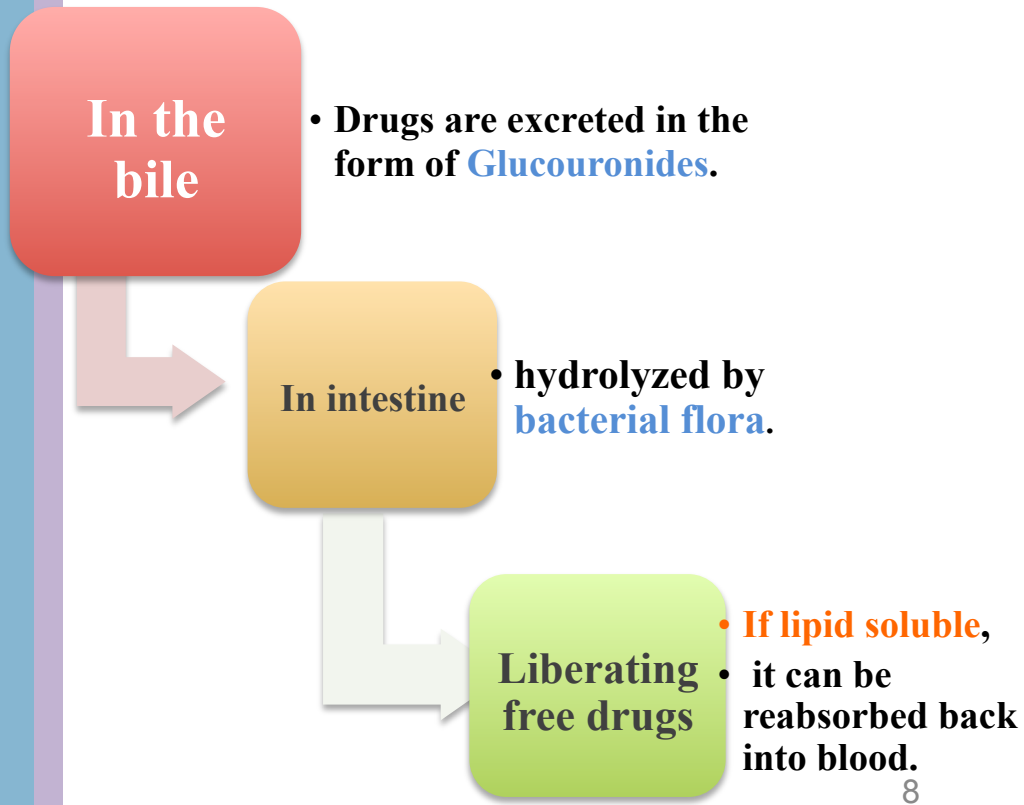
-Such drugs are secreted from the liver into bile by active transporters, then into duodenum.

-Some drugs undergo **enterohepatic circulation*** back into systemic blood circulation.

*entero=intestine, hepatic=liver, circulation=reabsorption

Enterohepatic Circulation

Prolongs the duration of action of drugs.
e.g. Digoxin, Morphine, Thyroxin.



Plasma half-life (t ½)

The time required for the plasma concentration of a drug to fall to half of its initial concentration.

It is a measure of duration of action and determine the dosing interval.

Drugs of SHORT plasma half life:
Penicillin, Tubocurarine.

Drugs of LONG plasma half life:
Digoxin, Thyroxin, Arsenic.

Factors that may increase half-life (t ½)

Decreased metabolism

Liver disease.

Microsomal inhibitors.

Decreased clearance*

Renal disease.

Congestive heart failure.

High binding of drugs

Plasma proteins.

Tissue binding.

Enterohepatic recycling

*Clearance is a measurement of Renal excretion

Loading Doses	Maintenance Doses
-It is an initial large dose of a drug that may be given at the beginning of a course of treatment before dropping down to a lower maintenance dose. -After administration of the drug, the plasma concentration decreases due to distribution of drug to other tissues. -It is used to achieve rapid therapeutic plasma level.	-Are the doses required to maintain the therapeutic level of the drug constant or the steady state of the drug "its given after the loading doses to maintain the effective level" e.g.: The patient needs to take regular doses of a drug such as Amoxicillin (500 mg) 8 hourly to maintain the therapeutic level.
These doses balances the drug Distribution	These doses balance the amount of drug lost during Metabolism and Clearance (excretion).

Clinical Application of Loading Dose*

A loading dose may be desirable if the time required to attain steady state of drug (4 elimination $t_{1/2}$ values) is long, and rapid-relief is required in the condition being treated.

For example, the $t_{1/2}$ of **Lidocaine** (treating Arrhythmia "irregular heartbeat") is usually 1-2 hours. Arrhythmias after myocardial infarction are life-threatening, and one cannot wait 4-8 hours to achieve a therapeutic concentration.

Use of a loading dose of Lidocaine in the coronary care unit is standard.

*males' slides.

Steady State Levels

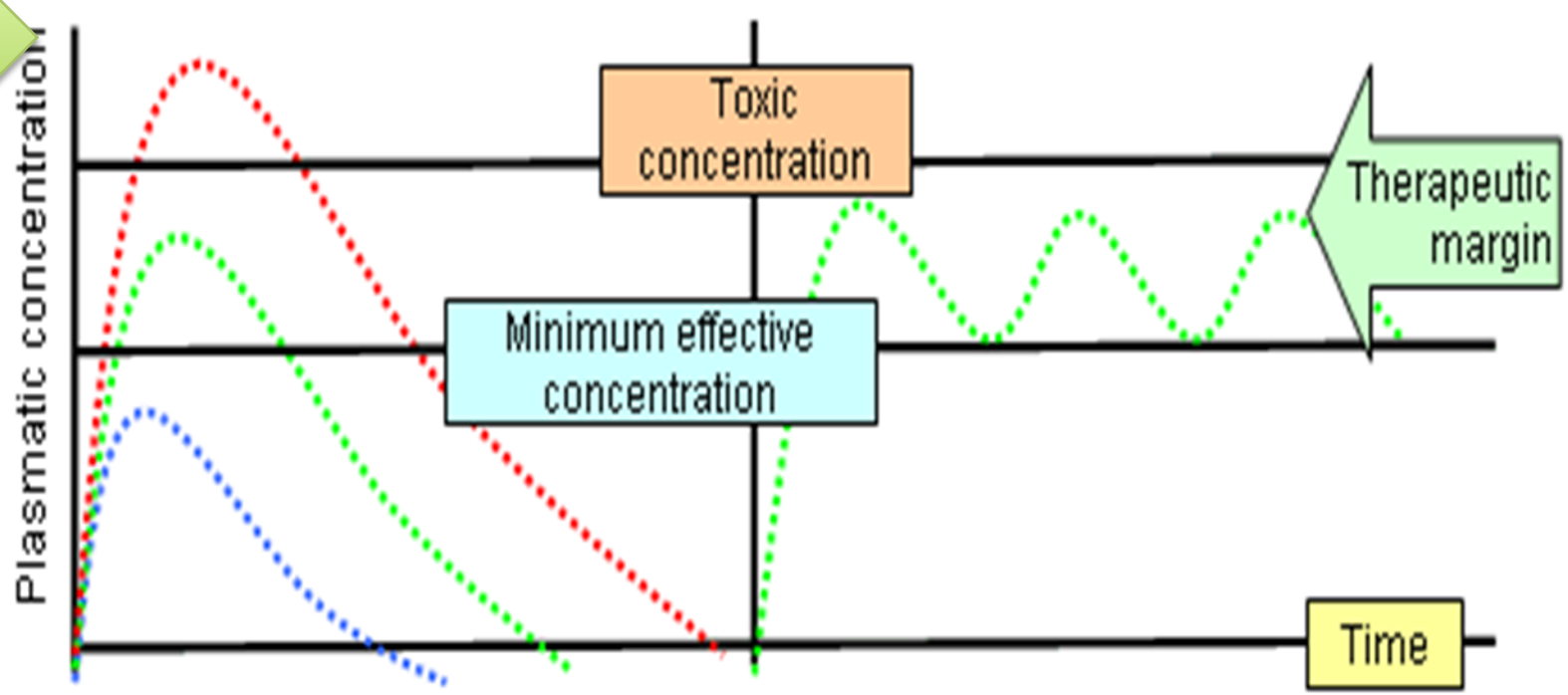
A state at which the therapeutic plasma concentration of the drug remains constant with the therapeutic window "the range between effective and toxic levels of drugs"

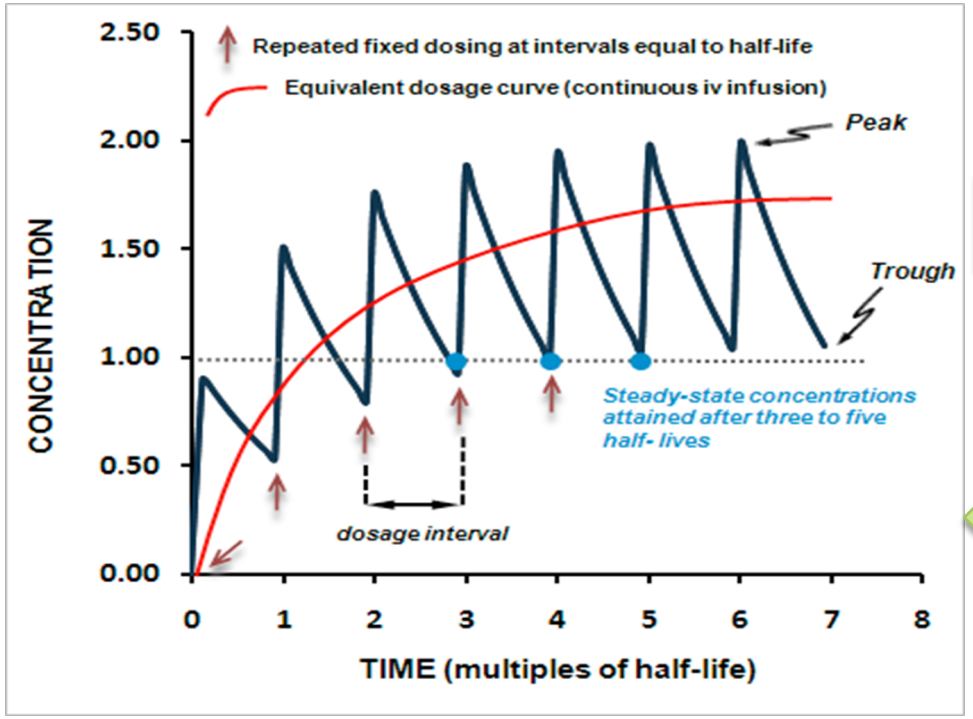
[Rate of drug **Administration** = Rate of drug **Elimination**]

In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion to maintain a steady-state concentration of drug associated with the therapeutic window (the range between effective and toxic levels of drugs).

Males' slides

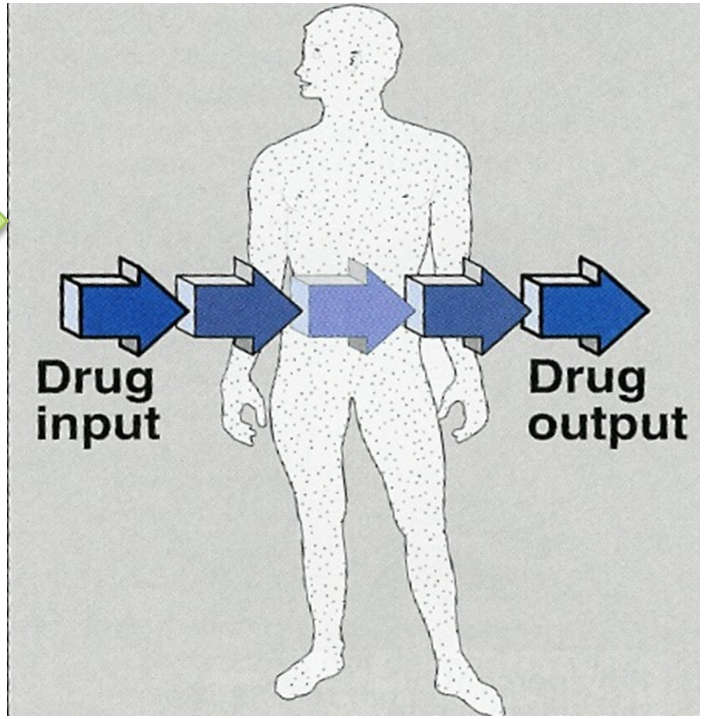
Therapeutic window





Steady state of a drug

Steady state levels



SUMMARY

Identify main and minor routes of Excretion.

***Main Routes of Excretion:**

A) Renal Excretion:

-Glomerular filtration.

Depends upon renal blood flow (600 ml/min).

-Passive tubular re-absorption.

In distal convoluted tubules & collecting ducts.

-Active tubular secretion.

in proximal tubules; increases drug concentration in lumen.

B) Biliary Excretion:

-Occurs to few drugs that are excreted into feces.

-Some drugs undergo enterohepatic circulation back into systemic blood circulation.

***Minor Routes of Excretion:**

Exhaled air (Exhalation), Salivary, Sweat, Milk, tears.

Describe enterohepatic circulation and its consequences on duration of drugs.

It prolongs the duration of action.

In the Bile: Drugs are excreted in the form of Glucouronides
Then in the Intestine: hydrolyzed by bacterial flora
Liberating free drugs : If lipid soluble, it can be reabsorbed back into blood.

Describe some pharmacokinetics terms :

Clearance of drugs:

Elimination of a drug from the body.

Biological half-life (t ½):

Is the time required for the plasma concentration of a drug to fall to half.

Multiple dosing:

drug is administered in Suitable doses by suitable route, with sufficient frequency that insures maintenance of plasma conc.

Steady state levels:

A state at which the therapeutic plasma conc. of the drug remains constant with the therapeutic window.

Maintenance dose:

Are doses required to maintain the therapeutic level of the drug constant or the steady state of the drug.

Loading dose:

A large initial dose that is given to achieve rapid therapeutic.

MCQS

1. The two most important sites for drug elimination:
A) pulmonary and liver
B) liver and gastrointestinal tract
C) kidney and liver
D) skin and liver

2……. of renal blood flow represents GFR :
A) 10%
B) 15%
C) 20%
D) 25%

3. Which of the following will have low concentration in the urine?
A) ionized drugs
B) hydrophobic drugs
C) water-soluble drugs
D) hydrophilic drugs
E) both A+B

4. Passive tubular re-absorption happens in:
A) glomerulus
B) proximal convoluted tubules
C) distal convoluted tubules
D) collecting ducts
E) both C+D

5. A person attempted suicide by taking an overdose of penicillin (pka: 2.74). which of the following you should give this person to eliminate the excess of penicillin by excreting it in the urine?
A) ammonium chloride to acidify the urine
B) ammonium chloride to alkalize the urine
C) sodium bicarbonate to acidify the urine
D) sodium bicarbonate to alkalize the urine

6. Which of the following increases when the lipid-soluble drugs undergo the enterohepatic circulation?
A) the drug's pH
B) the duration of action
C) the rate of excretion
D) the rate of metabolism

7. **Digoxin (long $t_{1/2}$) should be prescribed in:**
A) few doses a day
B) many doses a day
C) no doses at all
D) both A+C

1:C, 2:C, 3:B, 4:E, 5:D, 6:B, 7:A

MCQS

8. Half-life is decreased when there is:

A) a liver disease
B) a lot of microsomal inhibitors
C) a low plasma protein binding
D) a congestive heart failure
E) both A+B

9. The maintenance doses balance the amount of drug lost during:

A) Absorption
B) Distribution
C) Metabolism
D) Excretion
E) Both C+D

10. Steady state levels are maintained when:

A) rate of drug absorption = rate of drug excretion
B) rate of drug administration = rate of drug absorption
C) rate of drug administration = rate of drug metabolism
D) rate of drug administration = rate of drug excretion

8:C, 9:E, 10:D

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We hope that we made this lecture easier for you

Good Luck !