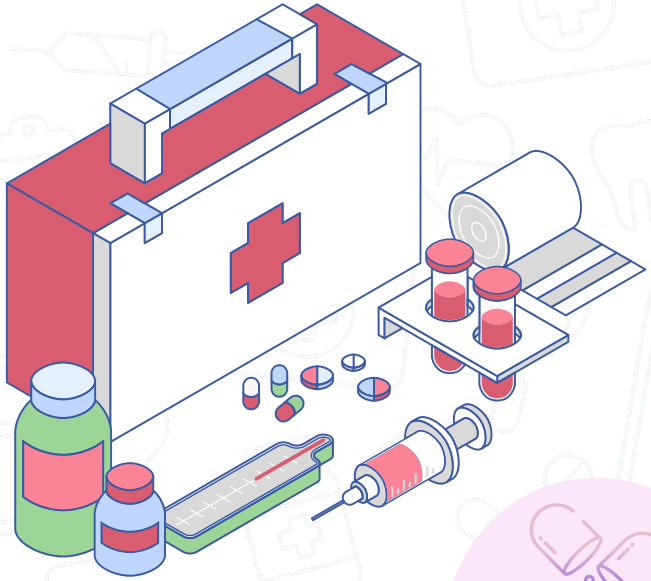
Click for useful **video**!



DRUG EXCRETION 442

EDITING FILE

Pharmacology
Team 442

Reviewed by Mohammad Amr Shaikha

Important
Main text
Male slide
Female slide
Extra info
Doctor notes

OBJECTIVES:

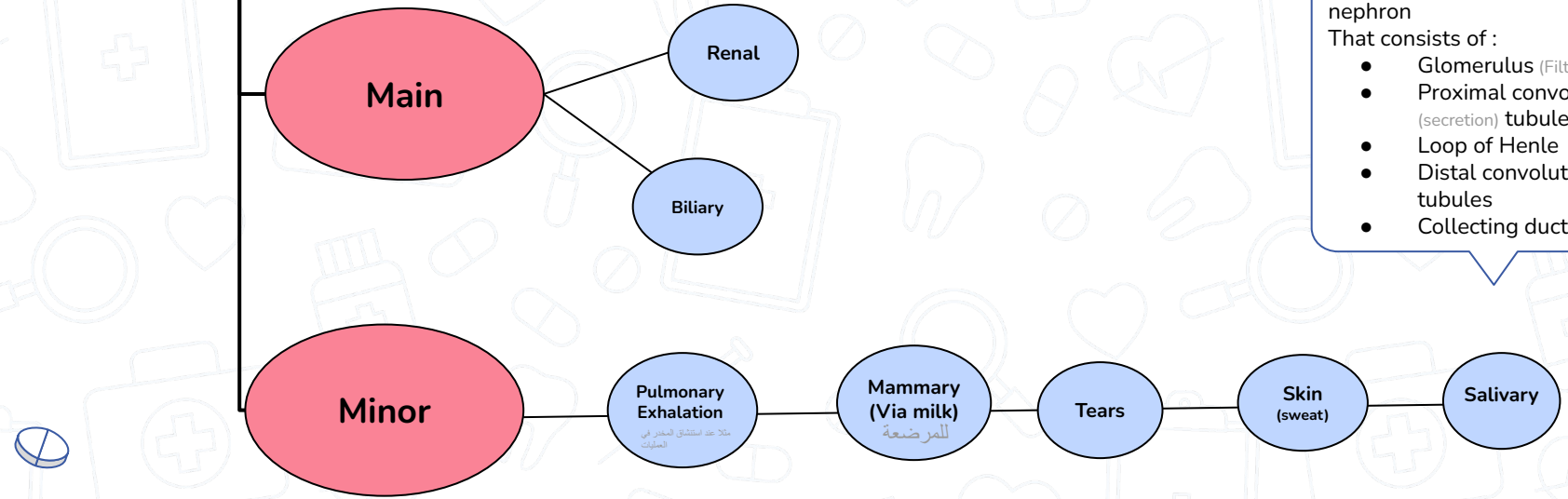
- Identify the main and minor routes of excretion including renal elimination and biliary excretion.
- Describe the enterohepatic circulation and its consequences on duration of actions of drugs.
- Describe pharmacokinetics terms including clearance of drugs, half-life (t 1/2), steady state levels, maintenance dose and loading dose.

Routes of excretion

The processes that determine the urinary excretion of drugs:

Renal Excretion= Filtration* – Reabsorption + Secretion*****

Glomerular filtration.* ***Passive tubular reabsorption.* ** Active tubular secretion.*



Structure of kidney:

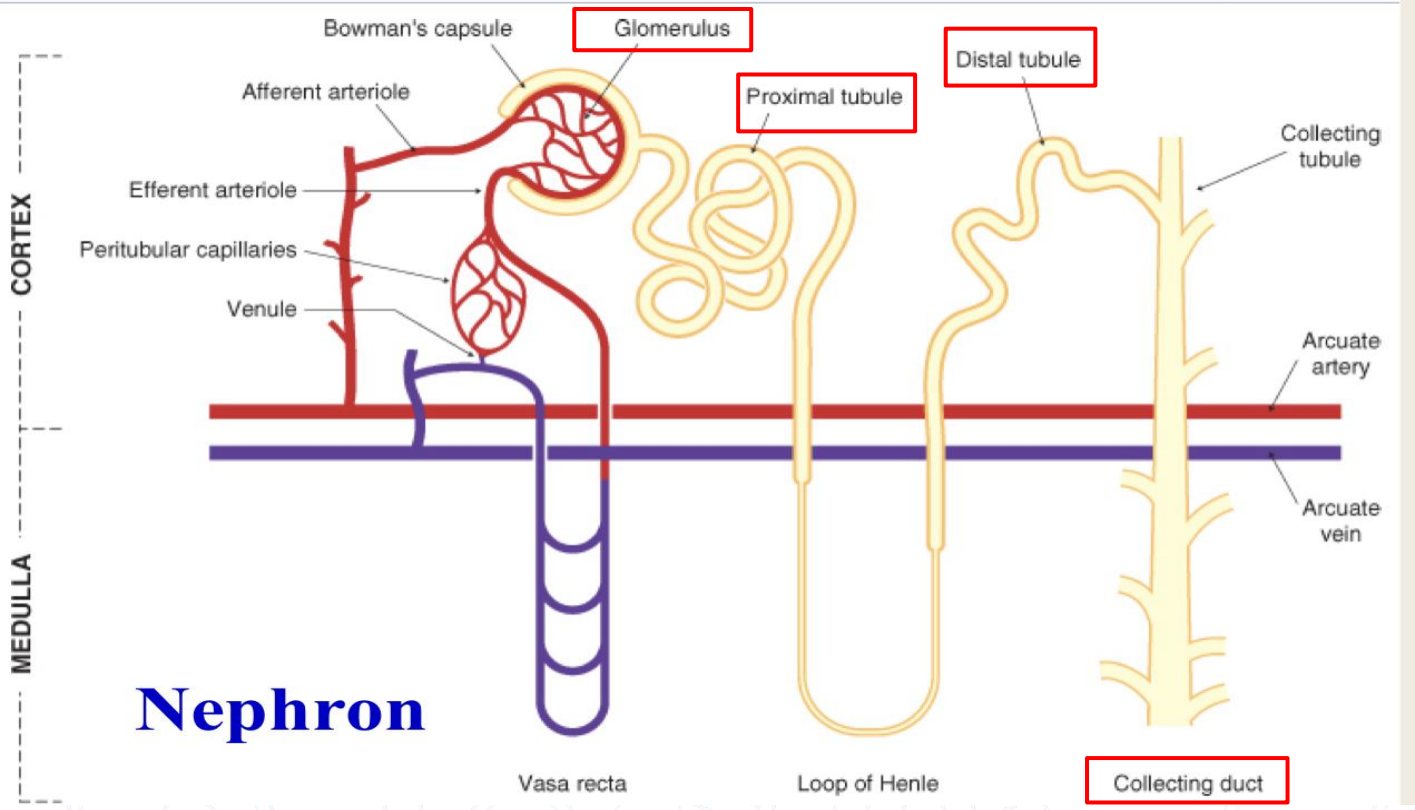
The structure unit of kidney is nephron

That consists of :

- Glomerulus (Filtration)
- Proximal convoluted (secretion) tubules
- Loop of Henle
- Distal convoluted tubules
- Collecting ducts

Structure of kidney

Glomerulus
-collection of blood vessels
-The site of filtration
-if the drug low+free it will be filtered and will continue moving
-it will be called filtrate



Two things will happen after filtration (adding-removing)
1-adding by tubular secretion
2-when it reach to its final result (urine) it will be reabsorbed
will discusses in detail next slides

Renal excretion

The principle process that determine urinary excretion of drugs

Glomerular Filtration Rate (GFR):

- Depends on renal blood flow (600 ml/min)
- GFR **20%** of renal blood flow= **125** ml/min.
- Glomerular filtration occurs to:

1. Low molecular weight drugs
2. free drugs (unbound to plasma proteins-easy process-)while bound drugs are not filtered.

large and bound will reabsorbed

Active tubular secretion:

- occurs mainly in proximal tubules; increases drug concentration in tubular lumen.
- organic **anionic** and cationic transporters mediate active secretion of anionic and cationic drugs. (specific-selective carrier-can be saturated)
- can **transport** drugs **against conc.** gradients.

E.g: Penicillin is actively secreted drug.

Passive Tubular Re-absorption: if it isn't water soluble

- In distal convoluted tubules & collecting ducts.
- Passive diffusion of unionized, lipophilic drugs.
- Lipophilic drugs can be **reabsorbed** back **from tubular lumen to blood circulation** **excretion** in urine will be **low.** لانه رجع للدم
- **Ionized** drugs are poorly reabsorbed so urinary **excretion** will be **high.**(because it is water soluble)

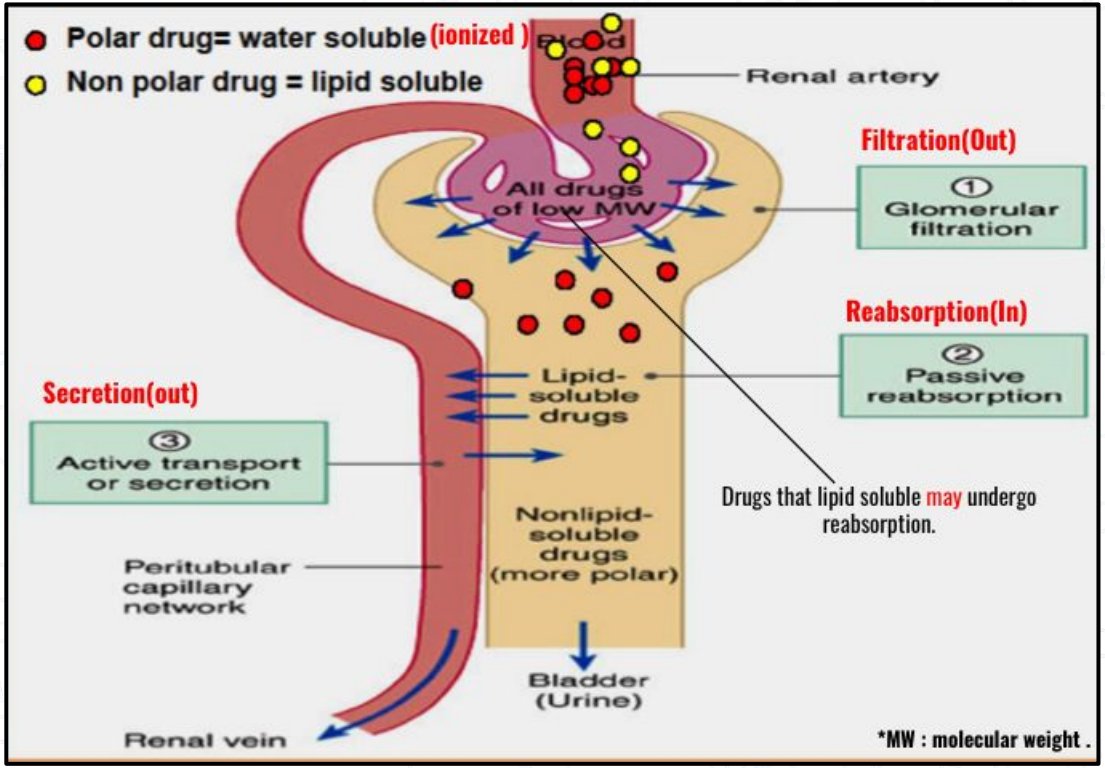
It has 2 systems
1- for acidic drugs
2- for basic drugs

Transporters for Acidic drugs:
1- Salicylates (aspirin)
2- sulphonamides
3- **Penicillin**
Transport of acidic drugs is blocked by **probenecid**
(used to slow down the rate of excretion so it will prolong duration-less frequency)

probenecid
- high affinity
-competitive drug
-acidic drug
drug-drug interaction
1-Probenecid bind to the carrier
2-penicillin reabsorbed
3- resulting in long duration for penicillin

Transporters for Basic drugs:
1- Morphine
2- Atropine
3- quinine
4- neostigmine
Names of basic drugs is NOT important
the suffix "ine" means that the drug is basic

RENAL EXCRETION (TOTAL OUT) = FILTRATION (OUT) - REABSORPTION (IN) + SECRETION (OUT)



*water soluble drugs = excreted easily

*Lipid soluble drugs = may need to be reabsorbed

-e.g no need to memories them

URINARY PH TRAPPING (STOPPING)

-drug ph doesn't change
-medium PH will change forcing drug to be execrated
-chemicals must have no side effect

Changing of pH urine by chemicals can either **enhance** or **inhibit** the renal excretion of drugs

Urine is **normally** slightly **acidic** and favours excretion of basic drugs (basic drugs are ionized/water soluble)

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

Acidification of urine by ammonium chloride (NH_4Cl) حفظ
Excretion of basic drugs
E.g.amphetamine

Alkalinization of urine by sodium bicarbonate ($NaHCO_3$) حفظ
Excretion of acidic drugs
E.g. Aspirin

Medium must be acidic(1-2)
So more basic drug can excreted via urine

- Acidic drugs: best **absorbed** in **acidic** medium + best **excreted** in **basic** medium
- Basic drugs: best **absorbed** in **basic** medium + best **excreted** in **acid** medium

Main routes of excretion

Renal excretion

Drugs **excreted** mainly by the **kidney**
1-**Aminoglycosides antibiotics** (as gentamycin)
2-B-lactam antibiotics as **penicillin**
3-Lithium
Memorize the red drugs only

Drugs should **prescribe carefully** for:
1-patients with **renal disease**.
2-**Elderly** people

There is 3 type of drugs
1-exerted by renal(urine)
2-excreted by biliary(faces)
3-both
you must take in consideration the drug routes
-e.g.if the patient has kidney disease don't give him drug that excreted by renal

Biliary excretion

Occurs to a few drugs that excreted into **faces** it has **two** types:

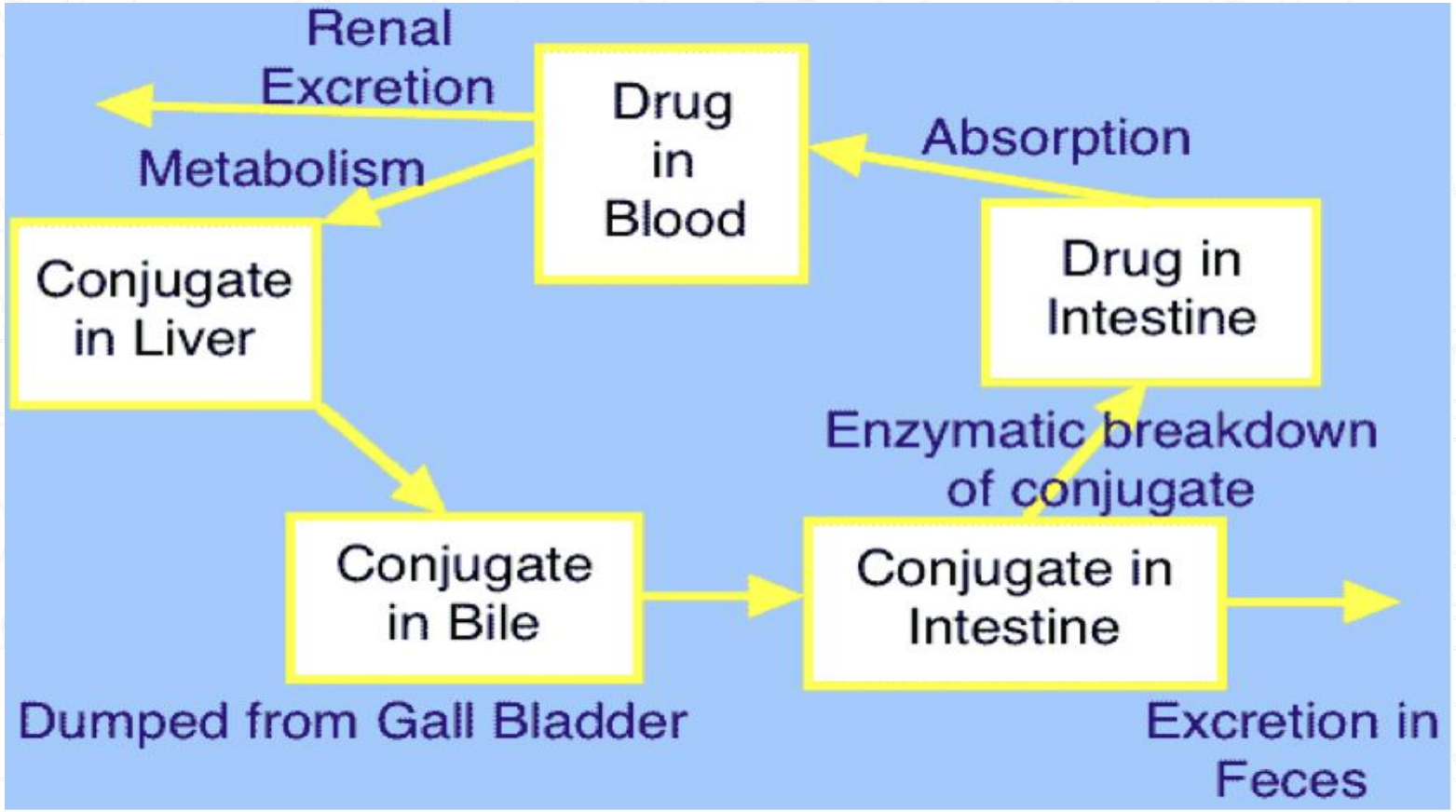
1) drugs are secreted from the liver into bile by **active transporters** then into **duodenum**.

Drug
1)in Bile
glucuronides
2)in intestine Hydrolyze by bacterial flora
Free drug
3)Reabsorbed back into blood

2) Some drugs undergo **Enterohepatic circulation** from intestine back into systemic blood circulation (where it move back through the hepatic portal vein towards the liver then back to the systemic circulation again)
Drugs excreted in the **bile** in the form of **glucuronides** will hydrolyze in intestine by **bacterial flora** liberating free drugs which can be reabsorbed back into blood if the drugs are lipid soluble
This prolongs the duration of action of drugs
e.g. digoxin, morphine, thyroxine
(Drug e.g. are NOT important)

EXCRETION

TO UNDERSTAND THE CONCEPT



PLASMA HALF-LIFE (T ½)

Definition is the time required for the plasma concentration of a drug to fall to half of its initial concentration. Is a measure of duration of action. Determine the dosing interval

➢ Factors that may increase half-life (t ½)

(They all cause drug staying in blood)

01	**Decreased metabolism**	• Liver disease. Absorption • Microsomal inhibitors. Drug-drug interaction
02	**Decreased clearance**	• Renal disease. • Congestive heart failure. low heart beat->less blood -> longer the drug stays in the body
03	**High binding of drugs**	• Plasma proteins. • Tissue binding.
04	**Enterohepatic recycling**	

med39 Decreased metabolism depends on enzymes
*Liver disease are also called hepatic disorder

Drugs of short plasma half life. (يعطي المفعول بوقت قصير مثلا ٥د ثم يطلع)

- E.g Penicillin G, tubocurarine.

Drugs of long plasma half life. (ياخذ وقت طويل على ما يعطي مفعول ممكن ١٢ ساعة)

- E.g Digoxin, thyroxine.

No need to memorise E.g

الفكرة انه عندي
Therapeutic window :-الي هي باختصار المستوى الي بيعالج
Steady state:- هو اني احافظ على هالمستوى طول فترة المرض لين يشفى-
Maintenance dose:هي الجرعة الي اخذها عشان احافظ على مستوى العلاج
مثلا

1. اخذت جرعة ٥مل
2. طلعت من جسمي وانا مابغد وصلت لمرحلة الشفاء
3. اخذ جرعة ثانية ٥مل

ادخال الدواء = اخراج الدواء

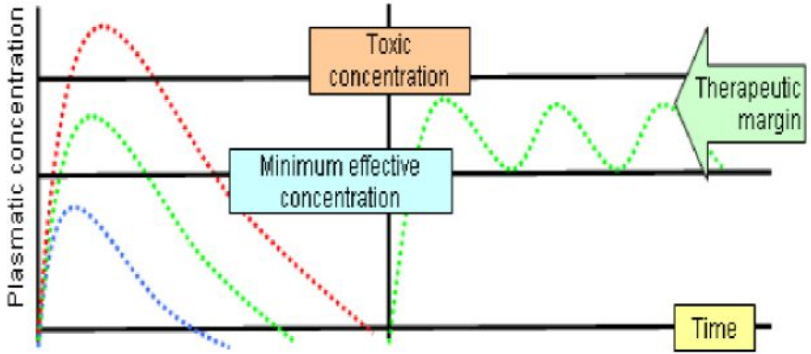
STEADY STATE LEVEL

- Steady state level: A state at which the therapeutic plasma concentration of the drug (mg/ml) **remains constant within the therapeutic window.**

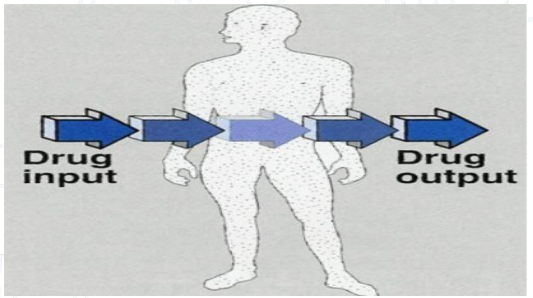
- Another definition: the amount of drug eliminated **equals** the amount of drug administered.

Med39 *What remains is the the range between the effective & attained after 3-5 half therapeutic

- Therapeutic window: the range between the effective and the toxic level of the drug.



Rate of drug administration = Elimination rate



STEADY STATE

- How many half-lives would be necessary to reach steady state?

Steady state concentration is attained after 3-5 half lives E.g. Morphine

E.g drug has 3 hour to reach its half-life
(3*3=9 |3*5=15)
Steady state is (9-15)

t ½ can be used to predict how long it will take from the start of dosing to reach steady-state levels during multiple dosing.

t ½=0 the start
Concentration of drug=100%

t ½=1
Concentration=50%

t ½=2
Concentration= 75%(25+50)

t ½=3
Concentration=87.5%
(37.5+50)

t ½=4
Concentration=94%
(43.8+50)

t ½=5
Concentration=97%
(47+50)

Dose 1
Dose 2
Dose 3
Dose 4
Dose 5

-50 ثابتة
-ازيد نص الي قبلها
مثلا عشان اطلع 3 اجمع ٥٠ الثابتة مع نصف ناتج الثانية (٢/٧٥=٣٧،٥)

LOADING DOSE VS MAINTENANCE DOSE

Maintenance dose	Loading dose
Are the doses required to maintain the therapeutic level of the drug constant or the .steady state of the drug	Is the large initial dose that is given to achieve .rapid therapeutic plasma level
These doses balance the amount of drug lost .during metabolism and clearance	After administration of the drug, the plasma concentration decreases due to .distribution of drug to other tissues
The patient needs to take regular doses of a drug such as amoxicillin (500 mg)/ 8 hours to .maintain the therapeutic level	-These doses balances the drug distribution -This is important for drugs with long half lives and emergencies
Maintenance dose= clearance x required plasma concentration No need to know just extra info	Loading doses= Vd x required plasma drug concentration No need to know just extra info

CLINICAL APPLICATION OF LOADING DOSE

- A loading dose may be desirable if the time required to attain steady state of drug (4 elimination t1/2 values) is long and rapid is required in the condition being treated.

- E.g.
1- t1/2 of lidocaine (antiarrhythmic drug) is usually 1-2 hours.
2- Arrhythmias after myocardial infarction are life-threatening, and one cannot wait more several hours to achieve a therapeutic concentration.

Steady state= 3-5 X 2 hour = 6-10 hours

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

SUMMARY

- Polar drugs are readily excreted and poorly reabsorbed.
- Lipid soluble drugs are reabsorbed back and excretion will be low
- Acidic drugs are best excreted in alkaline urine (sodium bicarbonate).
- Basic drugs are best excreted in acidic urine (ammonium chloride).
- Enterohepatic circulation prolongs half life of the drug.

1-CLICK THE LINK

2-CLICK "PHARMACOKINETICS DRUG ELIMINATION AND CLEARANCE ".

Click for useful **video**!

MCQ

Q-1 what is the main route of excretion?
A)renal B)Tear C)skin D)pulmonary
Q-2 dose that is given to achieve rapid therapeutic plasma level?
A)loading dose B) Maintenance dose C)oral dose
Q-3 Glomerular Filtration Rate (GFR) depend on?
A- low MW Drugs B- high MW Drugs C- bounded Drugs D- all Drugs
4) *Acidification* of urine done by ? (From the Dr)
A- sodium bicarbonate (NaHCO3) B-lidocaine C- penicillin D- ammonium chloride (NH4CL)

I-A
2-A
3-A
4-D

SAQ

Q-1 list 3 Factors that may increase half-life (t ½) ?

Q-2 What is the minor Routes of excretion ?

Answers

1-slide 10

2-slide 3

SAQ

Q-1 explain Enterohepatic circulation ?

Answers

1-slide 8

DONE BY THE AMAZING TEAM

You GOT THIS!

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