Pharmacology
Team 437

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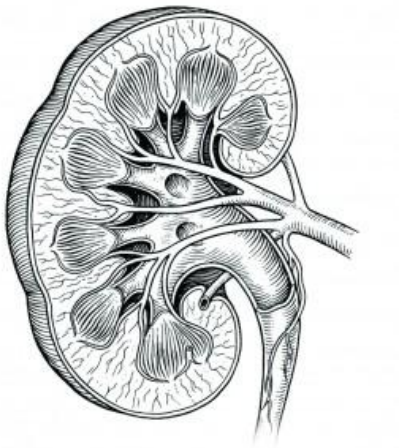


Renal Excretion of Drugs

Editing File

Objectives:

- Identify main and minor routes of excretion including renal elimination and biliary excretion.
- Describe its consequences on duration of drugs.
- Identify the different factors controlling renal excretion of drugs.
- Know the meaning of urinary ion trapping.
- Know how we can prescribe drugs in patients with renal impairment.

Important Notes Extra

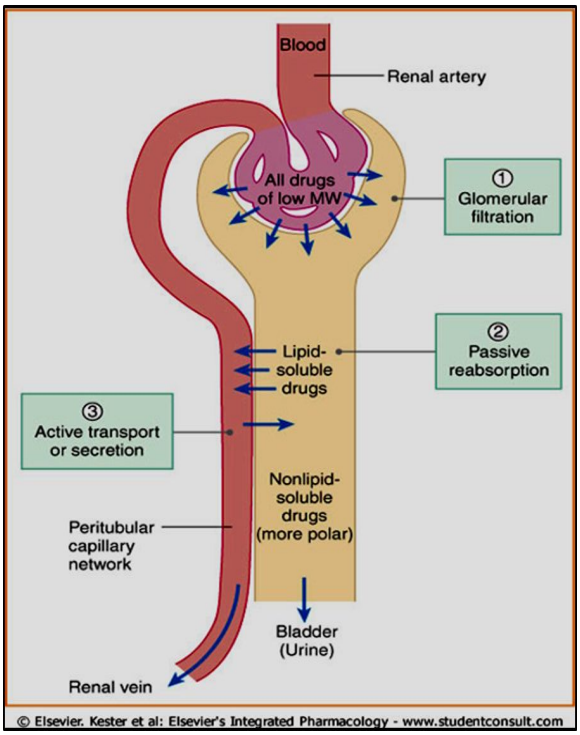
Routes of Excretion

Main Routes of Excretion:	Minor Routes of Excretion:
❑ Renal Excretion ❑ Biliary Excretion	❑ Pulmonary/Exhaled air (Exhalation) ❑ Salivary ❑ Skin/Dermal via sweat ❑ Milk (mammary gland) ❑ Tears

Structure of the kidney

The structural unit of the kidney is the nephron which consists of :

- Glomerulus
- Proximal convoluted tubules
- Loop of Henle
- Distal convoluted tubules
- Collecting ducts



Renal excretion of drugs occurs through

- Glomerular filtration
- Active tubular secretion
- Passive or active tubular reabsorption

Glomerular filtration (GFR)

- Depends upon renal blood flow (Normal GFR = 125-130 ml/min).
- GFR depends on hydrostatic pressure of blood flowing in the capillaries.
- Glomerular filtration occurs to :
  - Low MW drugs (most proteins have high MW and are not filtered)
  - Only free drugs (unbound to plasma proteins) are filtered. Why? if its protein bound it will be larger and unable to be filtered by the glomerulus
  - Polar or ionized or water soluble drugs are easily filtered e.g aminoglycosides. Why? So it can be easily dissolved in water.
  - Drugs with low volume of distribution i.e. it will not be anywhere except the blood or most of it will be in the blood, so it's concentration in blood is high and renal excretion is high vice versa high volume of distribution (Vd)

GFR is determined by creatinine, inulin. Inulin is easily filtered by kidney not reabsorbed .

It's important when prescribing drug thats excreted by kidney to check the GFR is normal, especially in older patients

Active Tubular Secretion

- Occurs mainly in proximal tubules and increases the drug conc. in lumen . Drugs undergoing active secretion have excretion rate values greater than normal GFR. It is especially important for secretion of ionized drugs into the lumen (e.g. Penicillin G) But didn't we say ionized drugs are easily dissolved? That's true but some can also be protein bound and therefore require active tubular transport to be secreted into the urine and excreted.
- General characteristics of active tubular secretion include;

1-carrier mediated (requires transporters) 2- saturable. 3-Requires energy 4-transports drugs against concentration gradients. 5-Non-specific (i.e competition may occur)

Types of Transporters

Transporters for organic acids

Aspirin
Penicillin
Sulfonamides
Probenecid

A PSP :)

Transporters for organic bases

Morphine
Catecholamines
Atropine
Quinine.

Aspirin increases uric acid by competition of transporter which causes gout.

Competitive Active Tubular Secretion of Drugs

- two structurally similar drugs having similar ionic charge and employing the same carrier- mediated process for excretion enter into competition.
- A drug with greater rate of excretion will retard the excretion of other drug with which it competes.
- The half life of both drugs is increased since the total sites for active secretion are limited.

Two drugs using the same carrier compete for excretion (non-specific) e.g probenecid increases half life of penicillin . There is competition between 2 acid/basic drugs on their corresponding transporter-this is used as an advantage to prolong duration of action of drugs but can also be harmful

Therapeutic advantages of competition:

- Probenecid inhibits active tubular secretion of organic acids e.g. Penicillin G (usually given parentally with only t1/2= 4hrs, so we need to delay the excretion for better effect), increases their plasma conc. 2 fold
- It suppresses the carrier mediated reabsorption of endogenous metabolite uric acid, prolongs duration of actoon of Penicillin G & increase its antibacterial action

Therapeutic disadvantages of competition

- Inhibition (renal tubular secretion) of nitrofurantoin by probenecid results in decreased efficacy of nitrofurantioin in UTIs
- الدواء يحتاج يكون بالمثانة فإذا ثبطنا إفرازه راح تقل فعاليته

Tubular reabsorption

- After glomerular filtration, drugs may be reabsorbed back from tubular lumen into systemic blood circulation.
- It takes place along all the renal tubules.
- Reabsorption increases half life of a drug.
- Reabsorption may be Passive or Active.

Passive Tubular Reabsorption	Active Tubular Reabsorption
In distal convoluted tubules & collecting ducts. Requires no energy.	Active Tubular Reabsorption (energy dependant).
❖ Passive diffusion of unionized, lipophilic drugs reabsorbed back into blood circulation and urinary excretion will be Low. ❖ Ionized drugs are poorly reabsorbed & so urinary excretion will be High.	❖ Occurs with endogenous substances or nutrients that the body needs to conserve. e.g. glucose, electrolytes, amino acids, uric acid. ❖ Probenecid inhibits active tubular re-absorption of uric acid. So, It increases excretion of uric acid in urine. ❖ Probenecid acts as a uricosuric agent in the treatment of gout.

Urinary pH trapping (Ion trapping)

Most of the drugs are weak acids or weak base, Changing pH of urine can inhibit or enhance the tubular drug reabsorption. This is used to enhance renal clearance of drugs during toxicity.

Urine is normally slightly acidic and favors excretion of basic drugs.

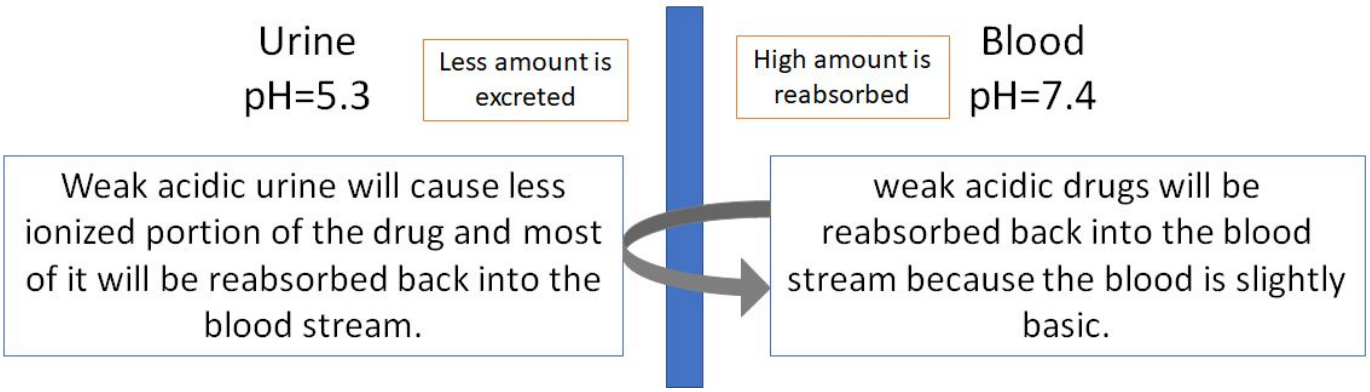
Urine pH varies from 4.5 to 8 depending upon the diet e.g meat causes more acidic urine and carbohydrates rich food may increase urinary pH.

Urine acidification	Urine alkalization
by ammonium chloride (NH_4Cl) increases excretion of basic drugs (amphetamine, gentamicin).	**by sodium bicarbonate $NaHCO_3$ increases excretion of acidic drugs (aspirin, barbiturates).**

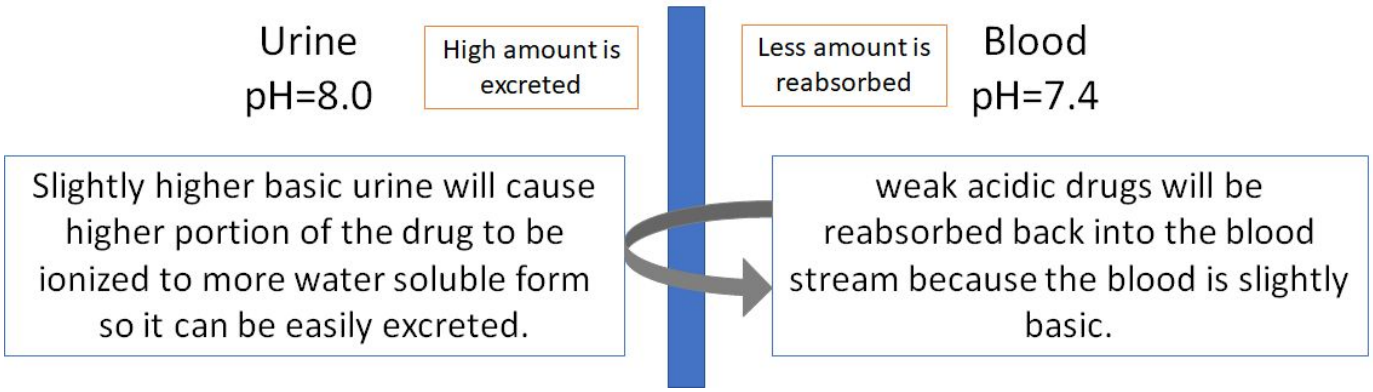
Ion trapping

Special thanks to team 436

- Urine pH varies (4.5 - 8.0).Consider a Barbiturate which is a weak acidic drug over dose.
- Well, normally most acidic drugs will be reabsorbed back into the blood stream.



- So, We need to alkalize the urine by sodium bicarbonate so that the drug can be ionized into more water soluble form and then easily excreted and weakly reabsorbed.



Drugs excreted mainly by the kidney

include:

- **Aminoglycosides antibiotics (Gentamycin)**
- **Penicillin**
- **Lithium** used for bipolar disorder **(mood stabilizer)**
- **Vancomycin**
- **Imipinem** broad spectrum beta lactam antibiotic **(champion antibiotic)**

These drugs may be contraindicated or need dose adjustment in these patients:

- **Renal disease.**
- **Elderly people**

Biliary Excretion

Occurs to few drugs that are excreted into feces

- e.g ceftriaxone and doxycycline are mainly excreted via bile and doesn't need dose adjustment in renal impairment. (Given for an infection in a renal failure patient)
- Some drugs undergo enterohepatic circulation back into systemic circulation

Drug renal clearance

- Creatinine clearance is the unit volume (ml) of plasma cleared by the kidney per unit time (min).
- Creatinine clearance (CrCl) is used as a marker instead of GFR.
- Clearance (ml/min)= $\frac{\text{Excretion rate (mg/min)}}{\text{Plasma concentration (mg/ml)}}$

- Renal clearance of many drugs and their metabolites depends on adequate renal function. Renal clearance is especially important for some drugs with narrow therapeutic index (e.g. lithium, digoxin, warfarin).

Decreased renal clearance may occur in

- Reduced renal blood flow: **Congestive heart failure. Hemorrhage, Cardiogenic shock**
  Decreased renal excretion : **Renal disease (e.g. glomerulonephritis).**
- This may increase half-life (t ½) of drugs

So what should we do in this situation?

- -Dose reduction of drugs is required to prevent toxicity especially with a narrow therapeutic index drugs. Dose adjustment is needed when the creatinine clearance is below 60 mL/min.
- Keep the usual dose but prolong the dosing intervals (e.g. gentamicin)
- Decrease the dose without changing dosing intervals (e.g. digoxin)

- Monitor blood level

Renal Excretion & Clearance

- Estimation of creatinine clearance
- The Cockcroft-Gault equation for creatinine clearance estimation:
- CrClest= estimated creatinine clearance, BW= body weight, Scr= serum creatinine
- Minor dose adjustment if CrClest is 30-60 mL/min, Major dose adjustment if CrClest less that 15 mL/min.

Male:

$$\text{CrClest} = \frac{(140 - \text{age})\text{BW}}{S\text{Cr} \times 72}$$

Female:

$$\text{CrClest} = \frac{0.85(140\text{-age})\text{BW}}{S\text{Cr} \times 72}$$

Physicochemical factors affecting renal excretion of drug

Molecular size	**Larger** molecular size of the drugs are more **difficult** to be excreted than smaller molecular size drugs, especially by glomerular filtration.
Lipophilicity (lipid solubility)	Urinary excretion is inversely related to lipophilicity. E.g. Increased lipid solubility → increase volume of distribution of drug (Vd) → decrease concentration of drug in plasma → decrease renal excretion.
Volume of distribution (Vd)	Renal clearance is inversely related to apparent volume distribution of drugs. i.e. A drug with large volume of distribution (more concentration in tissues, less concentration in plasma) is poorly excreted in urine. On the other hand, Drugs restricted to blood compartment (low volume of distribution) have higher excretion rates.
Plasma protein binding	Drugs that are bound to plasma proteins behave as **macromolecules** and cannot be filtered through glomerulus . - Only unbound form of drug (free form) appears in glomerular filtrate. - Protein bound drugs have long half lives (no excretion) Dr. Ishfaq slides: The renal clearance of drugs which are extensively bound to plasma proteins is increased after their displacement with another drugs. E.g. Gentamicin-induced nephrotoxicity by Furosemide (Furosemide displaces gentamicin from protein → more free drug accumulation in renal tissue)
Degree of ionization of drugs:	Increased ionization of drug increases its water solubility and thus enhances its renal excretion, Because **Polar drugs** (water soluble) are **easily filtered** e.g. aminoglycosides, tubocurarine.
Renal blood flow:	Adequate renal function depends upon renal blood flow, thus, renal blood flow is especially important for drugs excreted by Glomerular filtration. • **Increased** perfusion -Irrespective of the mechanism of excretion leads to increased contact of drug with secretary site and thus increased excretion. • **Decline** in renal blood flow can decrease excretion of drugs. NSAIDS especially non-selective (e.g. aspirin and ibuprofen) inhibit the production of prostaglandins (especially E & I which are protective for stomach and their inhibition=peptic ulcer) which dilate afferent arterioles and therefore reduce renal perfusion and GFR, thus decreasing excretion of drugs
Biological factors	**Age** can affect renal clearance: Renal clearance is reduced in neonates (because kidney and liver function not complete before 2 yrs) and elderly due to pharmacokinetic changes. Dose reduction is advisable, otherwise toxicity may occur.

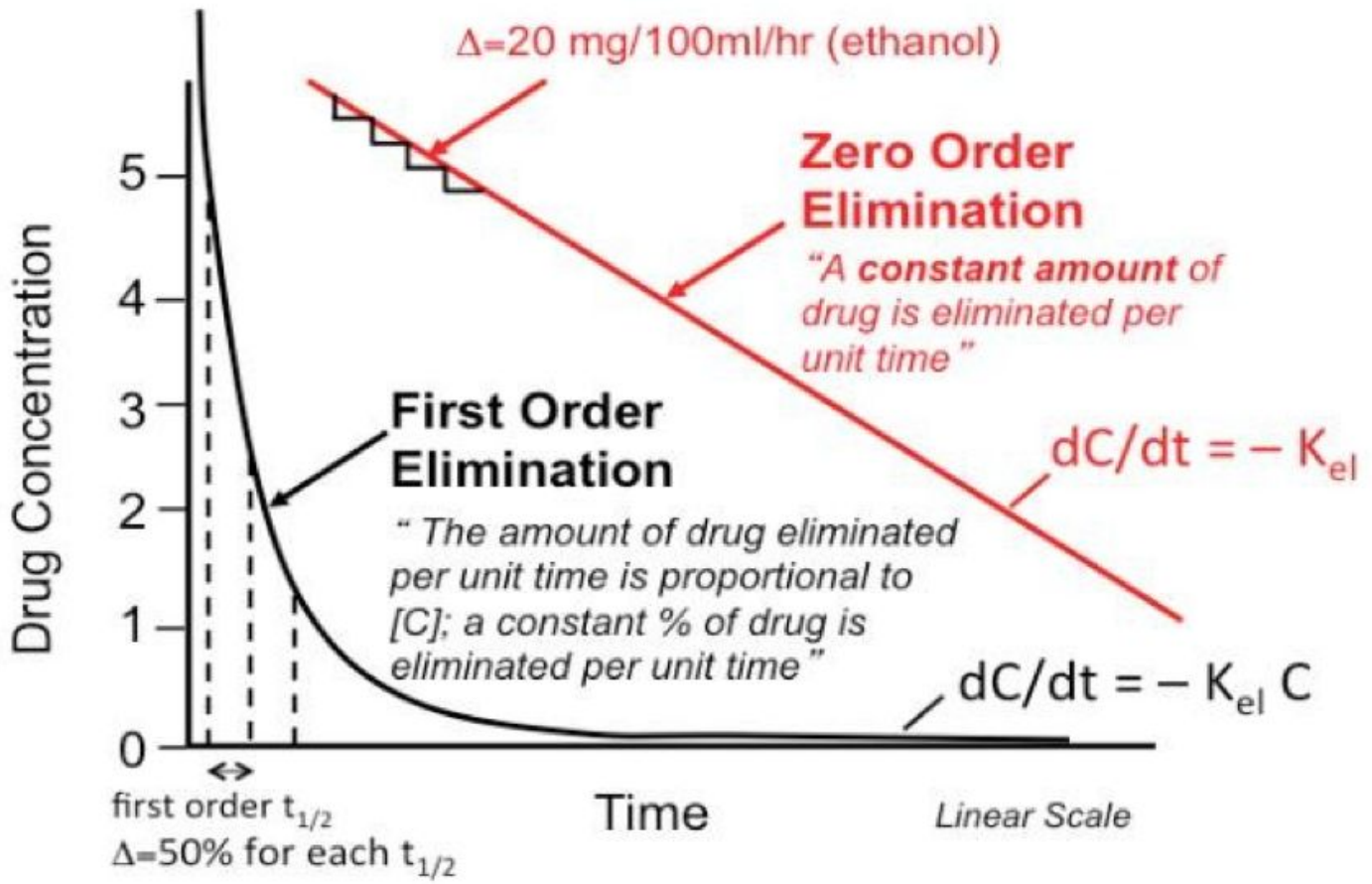
Physicochemical factors affecting renal excretion of drug (cont.)		
	Disease states	Impairs the elimination of drugs, thus may increase half-life (t ½) of drugs. This may occur due to: -Reduced renal blood flow. As in congestive heart failure, hemorrhage, and cardiogenic shock. -Decreased renal excretion, as in renal disease (e.g. glomerulonephritis)
	Urine pH	-Most drugs are weak acids or weak bases. -Normal urine pH = 5.3 (slightly acidic) and favors excretion of basic drugs. Urine pH varies from 4.5 to 8 depending upon the **diet** e.g. **meat** causes **more acidic urine** and carbohydrates rich food may increase urinary pH. -Most of acidic drugs will be reabsorbed back into body. -Changing the pH of urine can inhibit or enhance the passive tubular reabsorption of drugs: Urine acidification: by ammonium chloride (NH4Cl) increases excretion of basic drugs (amphetamine, gentamicin). Urine alkalization: by sodium bicarbonate NaHCO3 increases excretion of acidic drugs (aspirin, barbiturates) Acidic drugs best absorbed in acidic medium and excreted in basic medium Basic drugs absorbed in basic medium and excreted in acidic medium

Risk Factors for NSAIDs-Associated Acute Renal Failure

- Prostaglandins (PGs) have major role in the preservation of renal function when pathologic states compromise physiologic kidney processes.
- PGI2 and PGE2 antagonize the local effects of circulating angiotensin II, endothelin,vasopressin, and catecholamines that reduce renal circulation.
- Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction.
- A significant reduction in GFR can occur following administration of an NSAID to a patient with any underlying disease states (NSAIDs inhibit production of PGs)

Orders of Elimination

Zero-order	First-order
The half-life is …….. At two places on the curve	
Not equal	**equal**
Constant …… is lost per unit time	
Amount	**Percentage**
The rate of excretion is…….	
rate of excretion is independent of the concentration of drugs in the plasma. The enzyme is saturated by a high free drug concentration, and the rate of elimination remains constant, even if the dosage is increased, this may increase toxicity of drugs.	**rate of excretion is directly proportional with concentration of drug in plasma.** if the dose is increased, the excretion rate is increased, (that is, with each half-life, the concentration decreases constantly by 50%)
E.g. Ethanol(alcohol), phenytoin, aspirin	**E.g.** penicillin, aminoglycoside , quinolones



Questions

MCQs:

1- Which of the following choices depends directly on the clearance of drugs?

(A) Maintenance dose (B) Volume of distribution.

(C) Half life (D) a and c

2- If the urine ph increases then that will…..?

(A) Increase acidic drug reabsorption. (B) Decrease acidic drug secretion .

(C) Increase aspirin reabsorption. (D) None of the above.

3- If a drug with a 3-hours half life is given with an initial dose of 10mg/ml, assuming first-order kinetics, how much drug will be left after 6 hours?

(A) 1.5mg/ml (B) 2mg/ml

(C) 2.5mg/ml (D) 0mg/ml

4- One of the free order drugs are ?

(A) Quinolones (B) Aspirin

(C) Ethanol (D) Phenytoin

5- If there is no active tubular secretion and there is no passive tubular reabsorption then that will leave us with….?

(A) Active reabsorption (B) GFR

(C) Drug concentration (D) Nothing

6- Which elimination method involve a constant fraction of drug eliminated per unit time…?

(A) Zero-order elimination (B)first-order elimination .

(C) Major order elimination. (D) All of the above.

7- Which elimination method involve a constant amount of drug eliminated per unit time…?

(A) Zero-order elimination (B)First-order elimination.

(C) Major order elimination (D) All of the above

8- Active tubular secretion occur mainly in:

(A) Glomerulus (B) Proximal convoluted tubules

(C) Loop of Henle (D) Distal convoluted tubules

9-NSAIDs will…..?

(A) Decrease GFR (B) Increase GFR

(C) no change on GFR (D) Increase passive reabsorption

10- One of the physiological properties that will affect the drug clearance is ….?
Pharmacodynamics

(A) Age . (B) Renal blood flow.

(C) volume distribution (D) Cardiogenic shock.

Answers: 1d 2d 3c 4a 5b 6b 7a 8b 9a 10c

Questions

SAQ:

Case: a patient used atropine for a period of time then he noticed some toxic effects what method should we use to increase the clearance of atropine?

- Urine acidification method of Ion trapping

(a) what is the name of drug used ?

- Ammonium chloride

(b) what is the mechanism of action ?

- It will increase basic drug excretion by urine acidification.

2- Name three physiological properties that will affect clearance ?

1. Molecular weight
2. Drug distribution
3. Degree of ionization

3- Name five drugs excreted mainly by the kidneys?

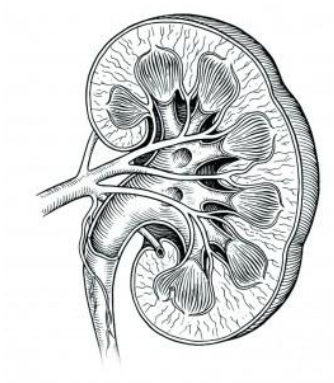
1. Aminoglycosides antibiotics (Gentamycin)
2. Penicillin
3. Lithium
4. Vancomycin
5. Imipenem

4- The enterohepatic circulation effect on drug half life is ?

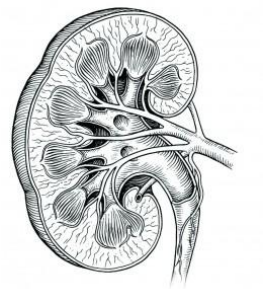
- Prolongation of half life.

what should we do to prevent drug toxicity in patients with renal problems?

A. Decrease dose
B. Dose adjustment
C. Prolong drug dosing intervals
D. Monitor drug level in blood



"It is not hard, you just made it to the end!"



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✓ Doctors' notes and slides

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