تفريغ فارما ١

اسم الموضوع: L13 :B blcker,CCB's,Duritics

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Soul Academy

لجان الدُفعات

B DRUGS

ADRENOCEPTOR ANTAGONISTS : β- Blockers

❑ Classification of β-adrenoceptor receptors

- ✓ β1-receptors (heart)
- ✓ β2-receptors (blood vessels, bronchioles)
- ✓ β3-receptors (adipose tissue).

❑ Mechanism of action

- ✓ Reduce cardiac output (via negative chronotropic and negative inotropic effects on the heart)
- ✓ Inhibit renin secretion
- ✓ Reduce sympathetic outflow from the central nervous system (CNS).

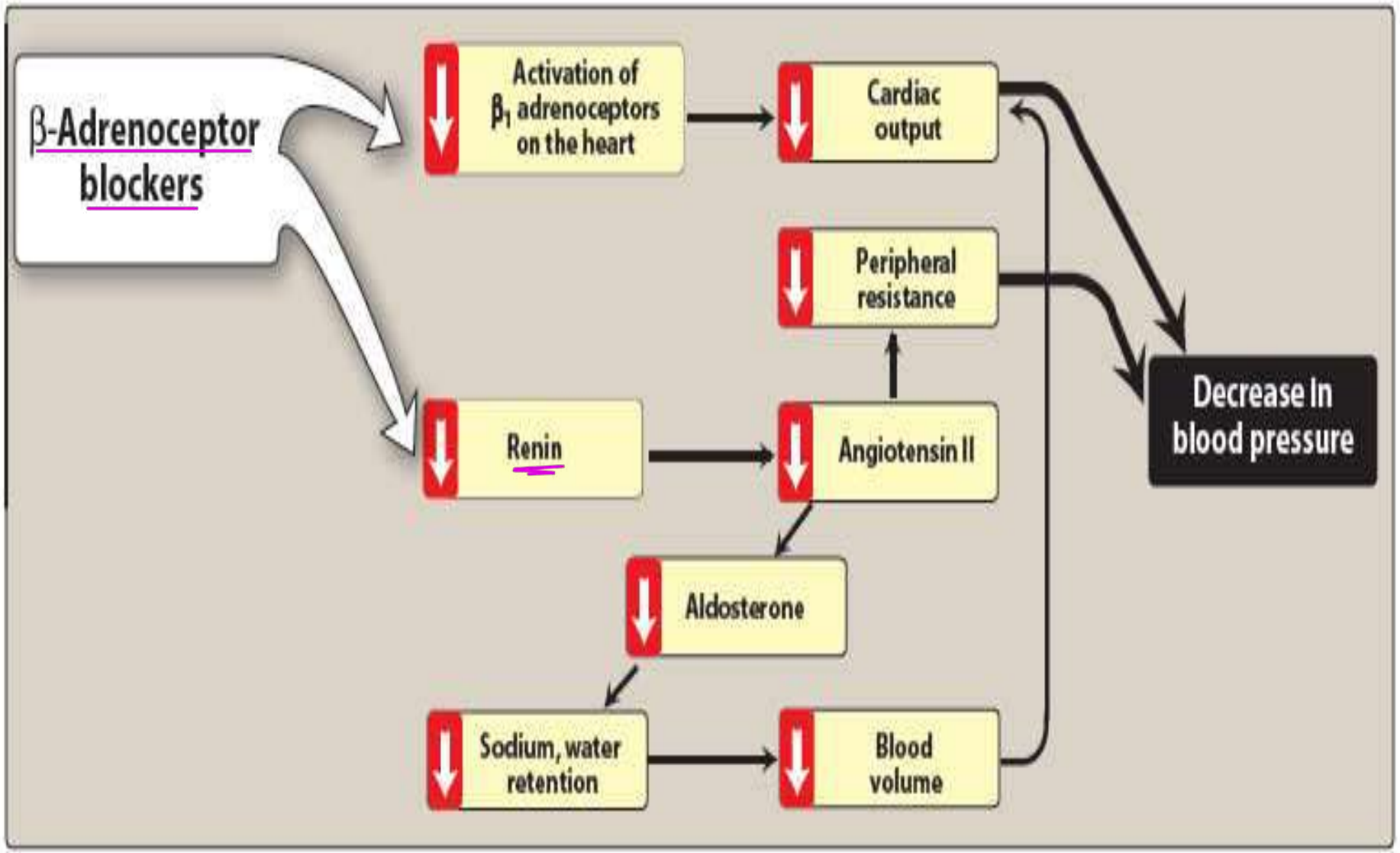
heart rate ↓

contractility ↓

Aliskiren بس مش زي الـ ما بشتغل بشكل direct هو مفعّل بعمل inhibition لـ release الـ renin

.

MOA


β-Adrenoceptor blockers
Activation of β1 adrenoceptors on the heart
Cardiac output
Peripheral resistance
Decrease in blood pressure
Renin
Angiotensin II
Aldosterone
Sodium, water retention
Blood volume

❑Pharmacokinetics

- well absorbed and active for hypertension orally

- Given intravenously in emergencies (Esmolol)

- Lipophilic drugs (e.g.**propranolol**) **are subject to extensive first pass metabolism**

non selective both β_1 & β_2

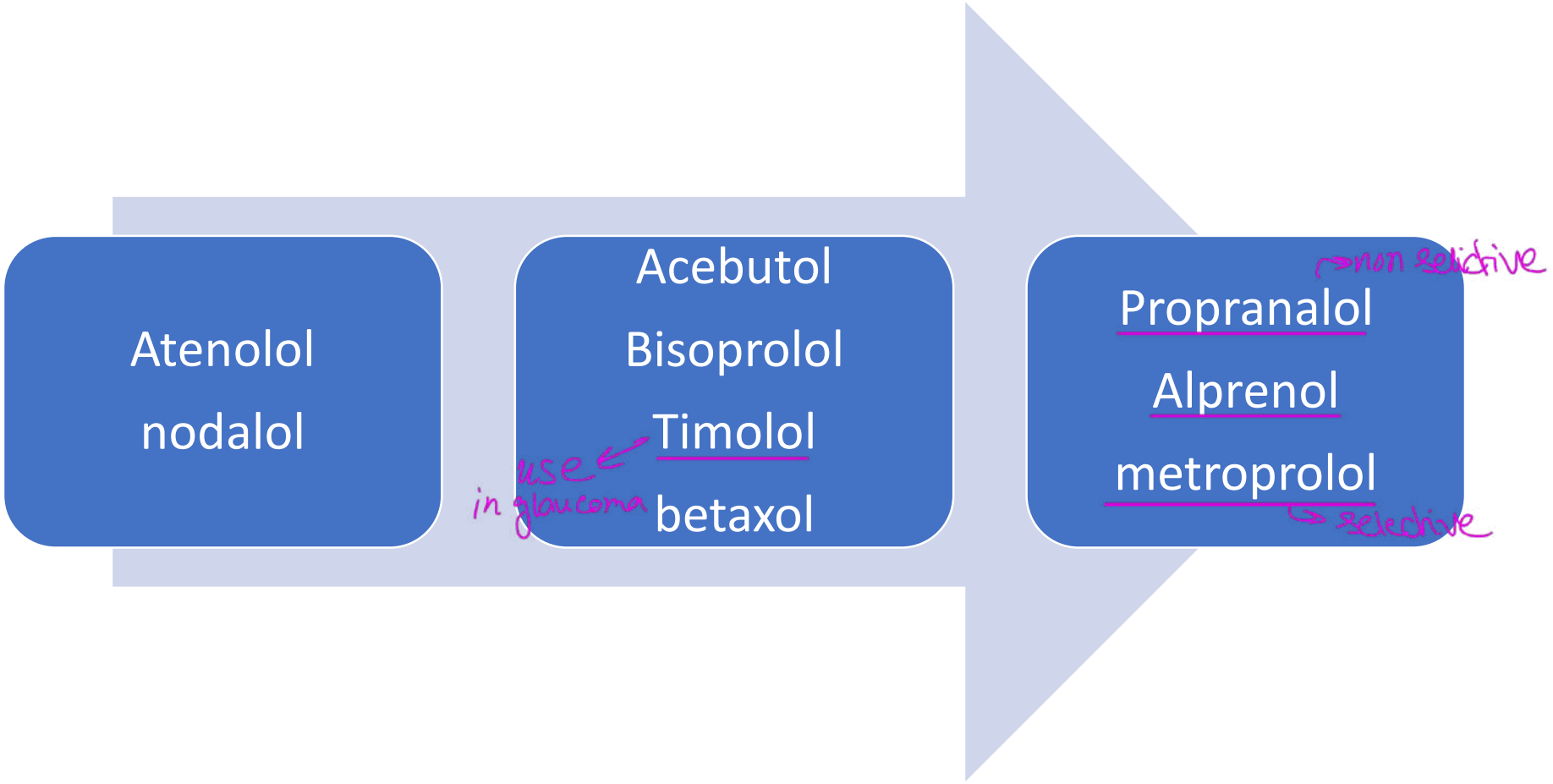
first pass metabolism يعني رح يصير عندي CNS sideeffect ورح يصير عندي

- Lipophilic beta-blockers enter the brain more readily than do polar drugs and so central nervous system side effects (e.g. nightmares, sedation, tremor) occur more commonly.

كوابيس

Classification of β- Blockers according to Increasing Lipophilicity

More lipophilic means more side effects (CNS)



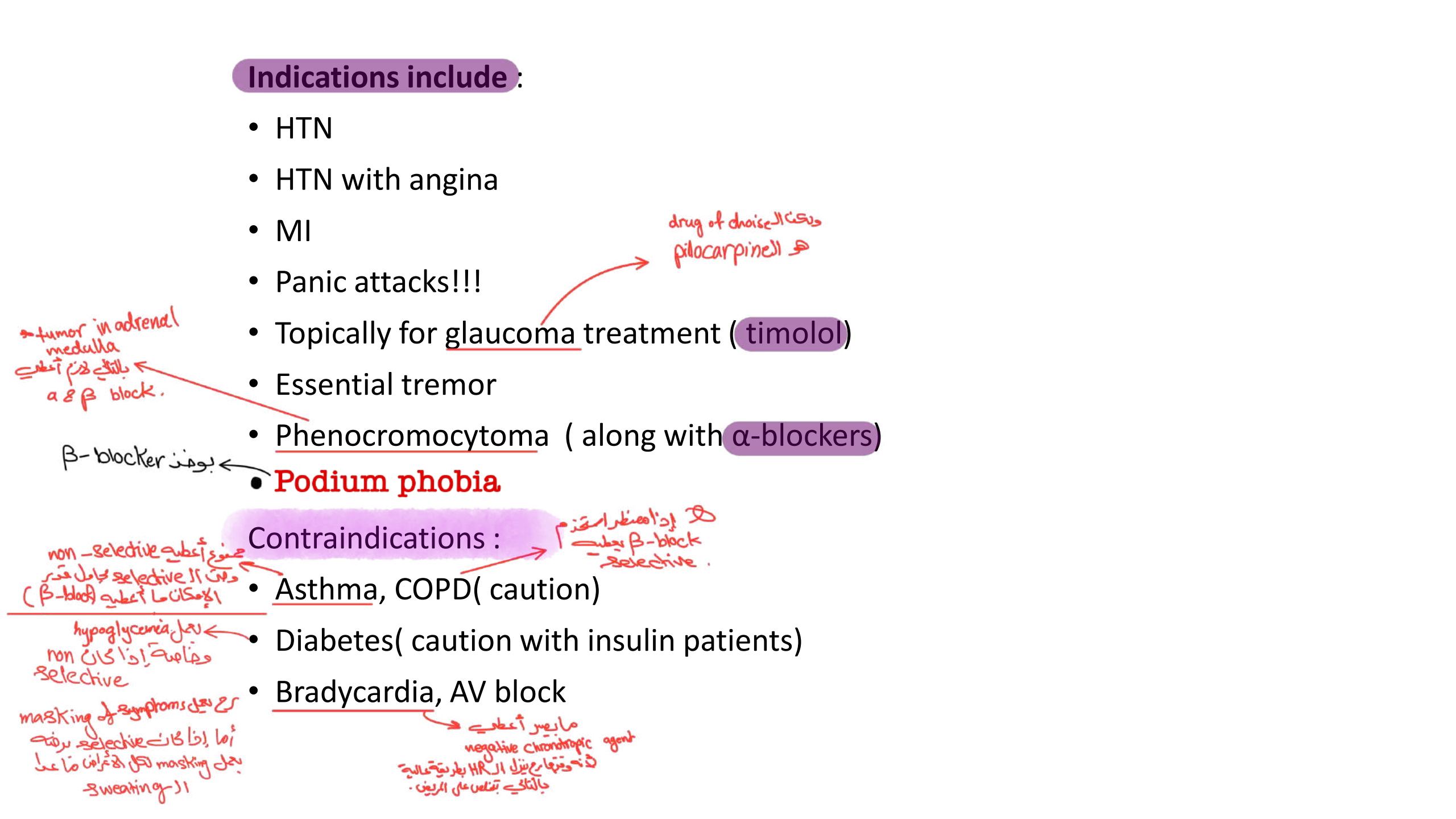
- Some beta-blockers (e.g. **oxprenolol**) **are partial agonists** and possess intrinsic sympathomimetic activity. drug acceptable when they have failed to tolerate a pure antagonist (e.g. patients with angina).
- Beta-blockers with additional vasodilating properties are available. This is theoretically an advantage in treating patients with hypertension. Their mechanisms vary. Some (e.g. **labetolol, carvedilol**) **have additional α-blocking activity.**
- **Nebivolol releases endothelium-derived nitric oxide**

Indications include:

- HTN
- HTN with angina
- MI
- Panic attacks!!!
- Topically for glaucoma treatment (timolol)
- Essential tremor
- Phenocromocytoma (along with α-blockers)
- **Podium phobia**

Contraindications :

- Asthma, COPD(caution)
- Diabetes(caution with insulin patients)
- Bradycardia, AV block



Adverse effects and contraindications :

- *Intolerance – fatigue*
- *cold extrémités* برودة الأطراف
- *erectile dysfunction;*
- *Airways obstruction*

(صعوبة في التنفس عند النوم) symptoms of HF يعني بلشت تظهر عندي dyspnea
بسبب انه صار عندي fluid overload . edema او chest ال تقبط.

- *Decompensated heart failure* – *β-adrenoceptor antagonists* are contraindicated

Signs:- Can be measured, seen, or tested

Symptoms:
- Cannot be measured or observed directly by others.
- Depend on the patient's perception and description.

- *Hypoglycaemia*

inhibition of glucagon release

- *Heart block* – *β-adrenoceptor antagonists can precipitate or* worsen heart block.

- *Metabolic disturbance* – *β-adrenoreceptor antagonists* worsen glycaemic control in type 2 diabetes mellitus.

Also increase in TG levels and reduction in HDL !!!

high-density lipoproteins

by blocks β_3

Drug interactions

- *Pharmacokinetic interactions:* *β-adrenoceptor antagonists* inhibit drug metabolism indirectly by decreasing hepatic blood flow secondary to decreased cardiac output. This causes accumulation of drugs such as **lidocaine** **that have** such a high hepatic extraction ratio that their clearance reflects hepatic blood flow.
- *Pharmacodynamic interactions:* *Increased negative inotropic* and atrioventricular (AV) nodal effects occur with **Verapamil**, **lidocaine** **and other negative inotropes.**

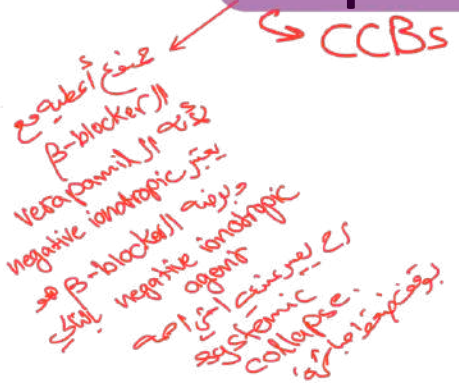


Table 28.1: Examples of β-adrenoceptors in clinical use

Drug	Selectivity	Pharmacokinetic features	Comment
Propranolol	Non-selective	Non-polar; substantial presystematic metabolism; variable dose requirements; multiple daily dosing	First beta-blocker in clinical use
Atenolol	β_1-selective	Polar; renal elimination; once daily dosing	Widely used; avoid in renal failure
Metoprolol	β_1-selective	Non-polar; cytochrome P450 (2D6 isoenzyme)	Widely used
Esmolol	β_1-selective	Short acting given by i.v. infusion; renal elimination of acid metabolite	Used in intensive care unit/theatre (e.g. dissecting aneurysm)
Sotalol	Non-selective (L-isomer)	Polar; renal elimination	A racemate: the D-isomer has class III anti-dysrhythmic actions (see Chapter 31)
Labetolol	Non-selective	Hepatic glucuronidation	Additional alpha-blocking and partial β_2-agonist activity. Used in the latter part of pregnancy
Oxprenolol	Non-selective	Hepatic hydroxylation/glucuronidation	Partial agonist

C DRUGS

CALCIUM-CHANNEL BLOCKERS

- Drugs that block voltage-dependent Ca channels are used to hypertension and angina.
- There are three classes:

➢ Phenylalkylamines: (Verapamil) target mainly cardiacmyocytes

➢ Benzothiazepines : (Diltiazem) target mainly cardiacmyocytes

➢ Dihydropyridines : (Amlodipine,Nifedipine) relax smooth muscles blood vessels

- **Mechanism of action (vasodilators)**

➢ Calcium-channel blockers inhibit Ca2 influx through voltage-dependent L-type calcium channels.

long

➢ Calcium-channel blockers therefore relax arteriolar smooth muscle, reduce peripheral vascular resistance ↓DBP and lower arterial blood pressure.

- **Pharmacokinetics**

➢ absorbed when given by mouth.

➢ **Nifedipine has a short half-life and many of its** adverse effects (e.g. flushing, headache) relate to the peak plasma concentration. Slow-release preparations improve its profile in this regard.

(time needed to eliminate 50% of the drug) العمر النصفي للدواء يعني يطلع منه 50%

لما احكي T-half قليل معناها الـ action سريع يعني الدواء يطلع من الجسم بسرعة.

أغلب أدوية الـ CCB's هيك

يعني إذا دواء كان الـ T-half مثلا 24 ساعة بالتالي بدي ضل أيام عشان أشوف التأثير تبعه يعني رح يظل بالجسم لفترة طويلة.

لما يكون الـ T-half للدواء طويل هاد بنعكس على كم مرة رح أعطي الدواء باليوم الـ (frequency)

لذلك كل ما كانت الـ T-half قليل معناها أنا بحاجة لـ doses أكثر ويكون برضه يعني أنا بحاجة أعطي جرعات أكثر والـ effect رح أحصله بوقت أكثر معناها الـ adverse effect بوقت أسرع.

DHP، الي بشتغل على blood vessels

عشان هيك أغلب أدوية الـ CCB's هي sustained release

المقصود فيها أنه كمية الدواء الي تطلع من الحبة بكميات قليلة من باب يظل مفعوله داخل الجسم والـ side effects تتأخر شوي

Dihydropyridines

- **Amlodipine is renally eliminated and** has a half-life of two to three days and produces a persistent antihypertensive effect with once daily administration

❖ *Dihydropyridine calcium-channel blockers* :

✓ ***Amlodipine*** **:**

- most prescribed CCB
- Stands on strong evidence , to improve mortality and morbidity
- Acheives slow rate to release , (less side effects)
- Once daily (5-10) mg per day

- **Adverse effects of CCB s :**
  - usually well tolerated,
  - Short-acting preparations (e.g. **nifedipine capsules) cause** flushing and headache (reflex tachycardia in some cases)

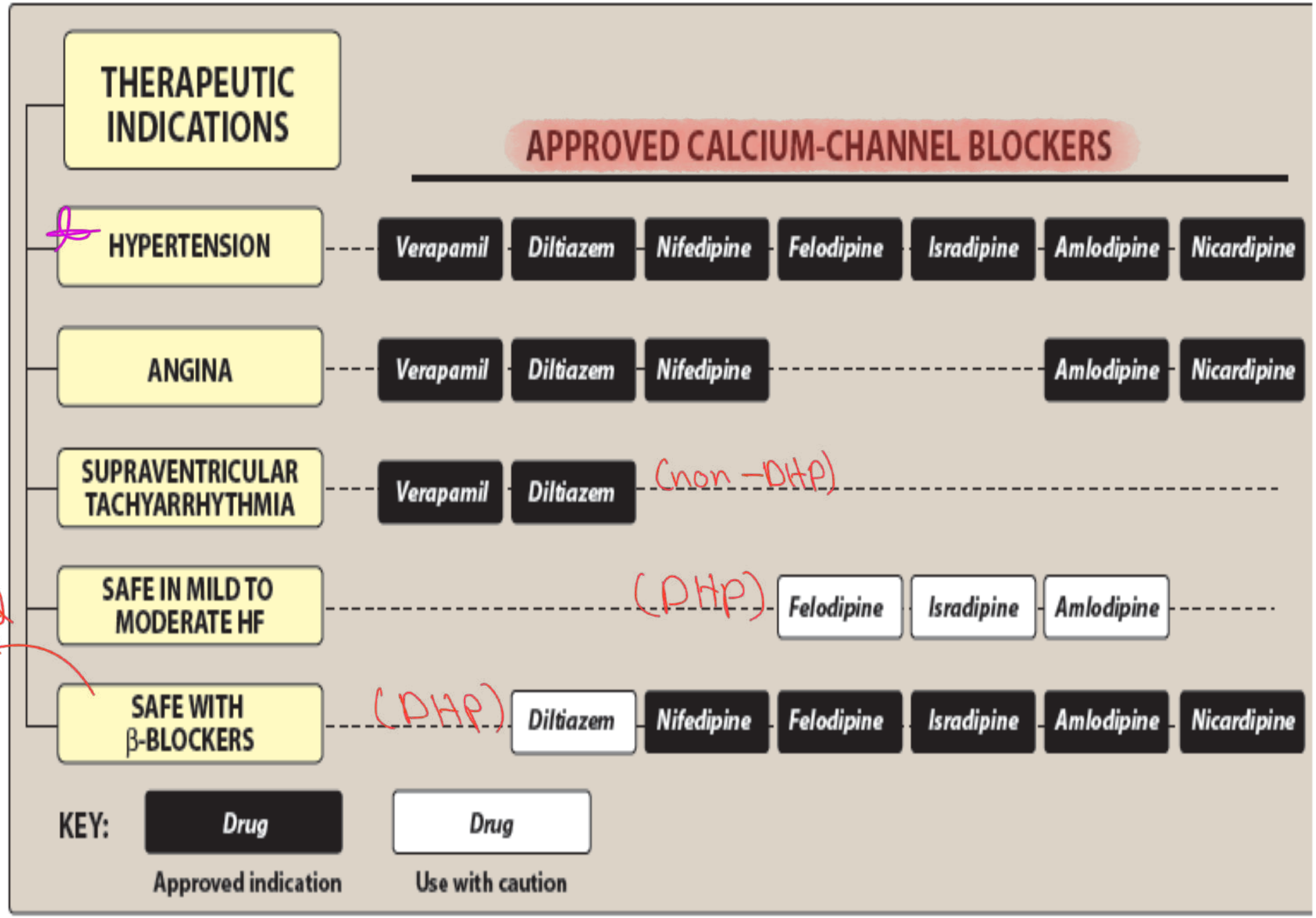
- Ankle swelling (oedema) is common .
- The negative inotropic effect of **verapamil exacerbates** cardiac failure.
- Constipation is common with **verapamil.**

Drug interactions

Intravenous **verapamil can cause circulatory collapse in patients** treated concomitantly with β-adrenoceptor antagonists.

Table 28.2: Examples of calcium-channel blocking drugs in clinical use

Class	Drug	Effect on heart rate	Adverse effects	Comment
Dihydropyridine	Nifedipine	↑	Headache, flushing, ankle swelling	Slow-release preparations for once/twice daily use
	Amlodipine	0	Ankle swelling	Once daily use in hypertension, angina
	Nimodipine	↑	Flushing, headache	Prevention of cerebral vasospasm after subarachnoid haemorrhage
Benzothiazepine	Diltiazem	0	Generally mild	Prophylaxis of angina, hypertension
Phenylalkylamine	Verapamil	↓	Constipation; marked negative inotropic action	See Chapter 32 for use in dysrhythmias. Slow-release preparation for hypertension, angina



Verapamil contraindecated with β Blockers

D DRUGS

DIURETICS

weak acids أغلبها هي

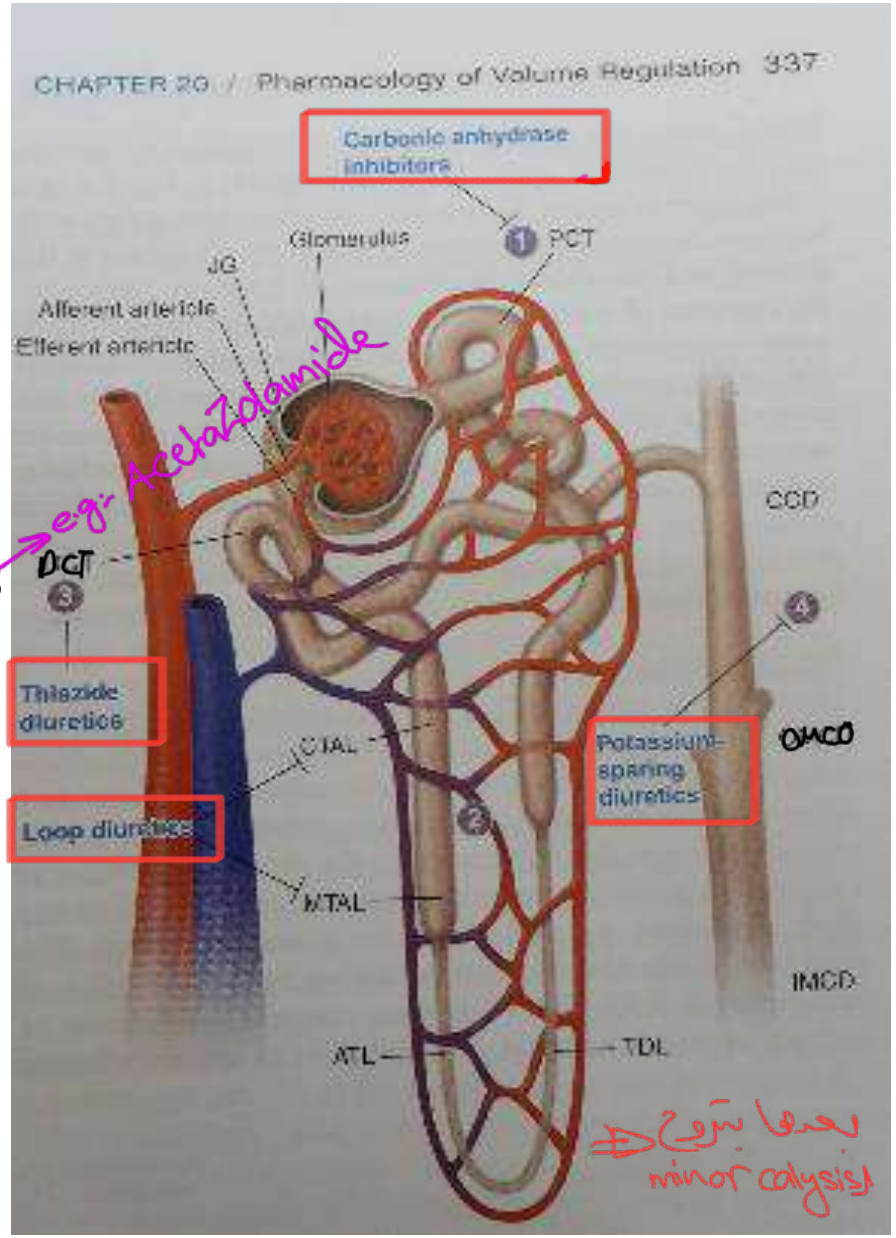
هي بشتغلوا على مبدأ
أنه إذا بدي أقلل BP لازم أقلل
من الـ blood volume
عن طريق
Na+ اللي أطلعن منه water وأطلعن
وأطلعن منه ك .

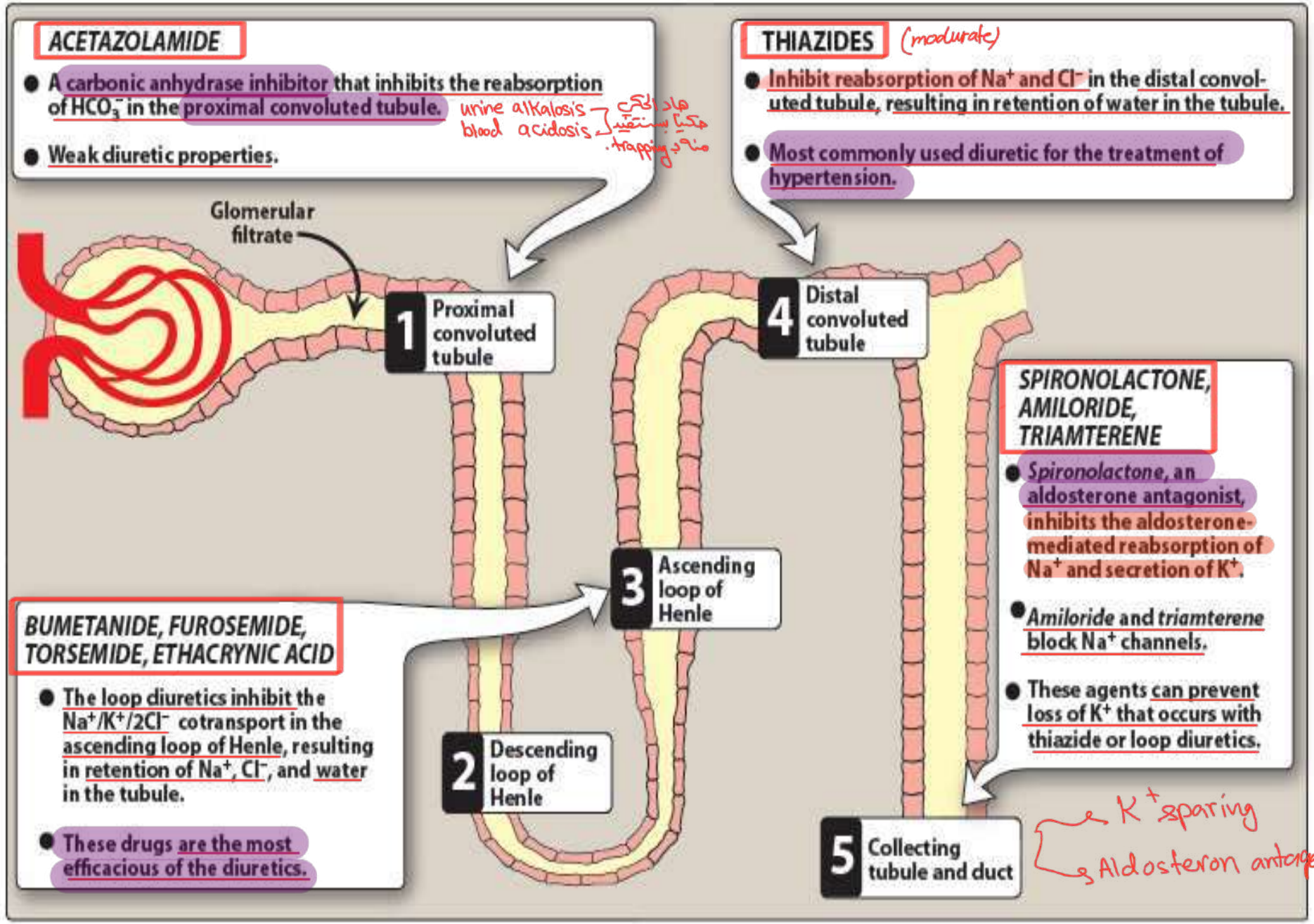
PRINCIPLES OF DIURETIC ACTION

- Increase the rate of excretion of Na^+ (natriuresis) and of an accompanying anion, usually Cl^-.
- Most clinical applications of diuretics are directed toward reducing extracellular fluid volume by decreasing total-body NaCl content.

Classes of Diuretics :

- Loop diuretics (high ceiling)
- Thiazides (moderate ceiling)
- Potassium Sparing
- Aldosterone antagonists
- Carbonic anhydrase inhibitors
- Osmotic diuretics




ACETAZOLAMIDE
A carbonic anhydrase inhibitor that inhibits the reabsorption of HCO_3^- in the proximal convoluted tubule.
Weak diuretic properties.
urine alkalosis
blood acidosis
THIAZIDES (moderate)
Inhibit reabsorption of Na^+ and Cl^- in the distal convoluted tubule, resulting in retention of water in the tubule.
Most commonly used diuretic for the treatment of hypertension.
Glomerular filtrate
1 Proximal convoluted tubule
2 Descending loop of Henle
3 Ascending loop of Henle
4 Distal convoluted tubule
5 Collecting tubule and duct
BUMETANIDE, FUROSEMIDE, TORSEMIDE, ETHACRYNIC ACID
The loop diuretics inhibit the $Na^+/K^+/2Cl^-$ cotransport in the ascending loop of Henle, resulting in retention of Na^+, Cl^-, and water in the tubule.
These drugs are the most efficacious of the diuretics.
SPIRONOLACTONE, AMILORIDE, TRIAMTERENE
Spironolactone, an aldosterone antagonist, inhibits the aldosterone-mediated reabsorption of Na^+ and secretion of K^+.
Amiloride and triamterene block Na^+ channels.
These agents can prevent loss of K^+ that occurs with thiazide or loop diuretics.
K^+ sparing
Aldosteron antagonist

Solute transport and reabsorption sites

diuretics كل الـ
weak acid
internally/locally يشتغلوا

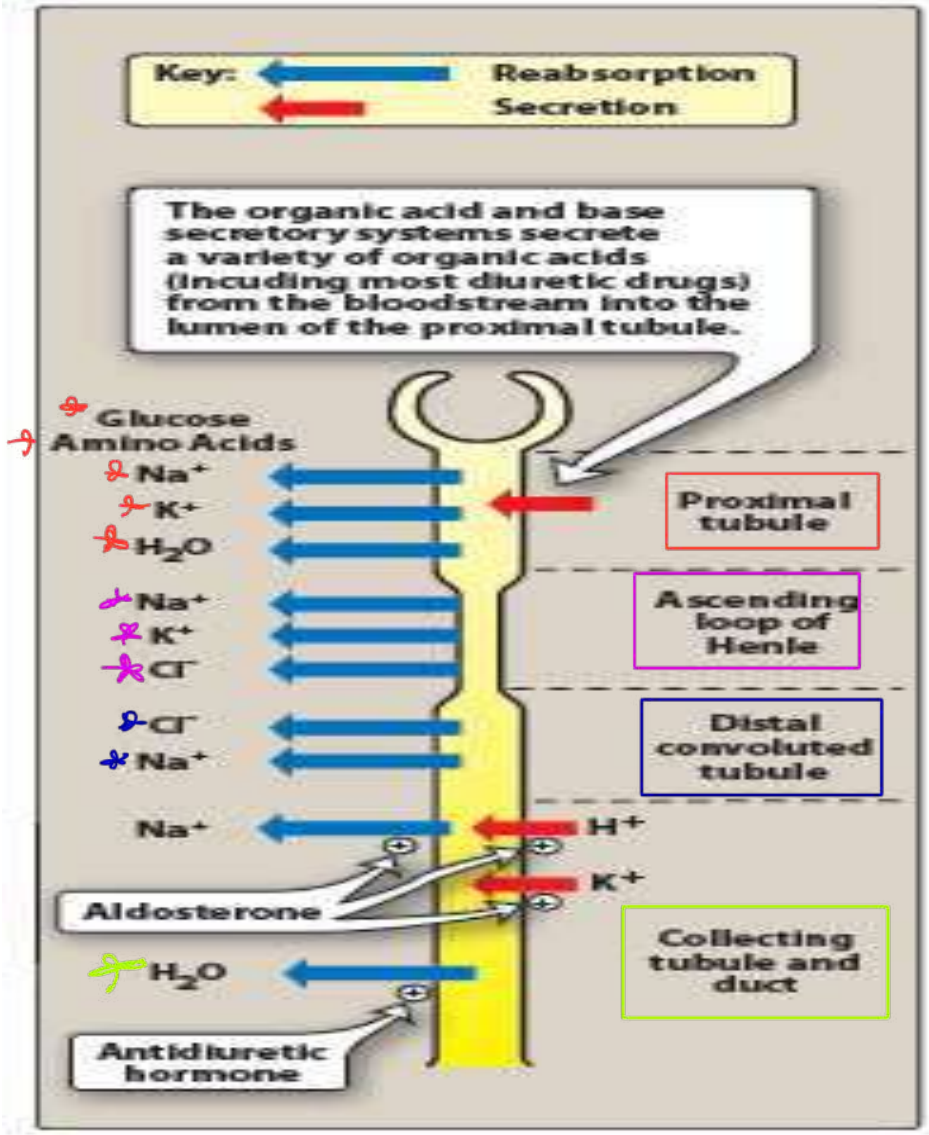


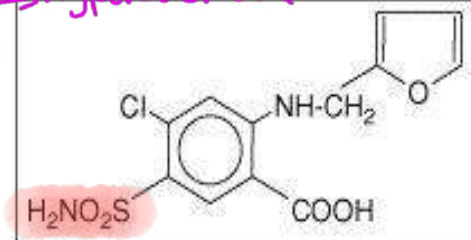
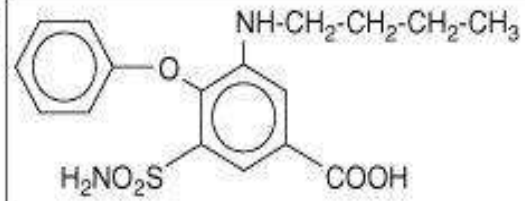
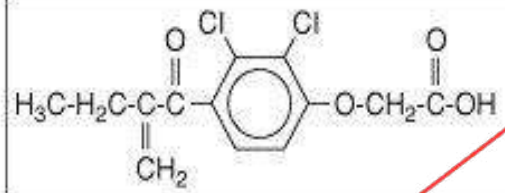
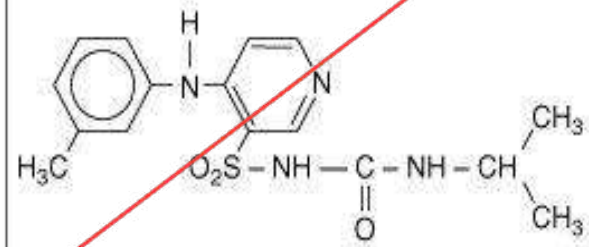
Figure 22.3
Sites of transport of solutes and water along the nephron.

Loop Diuretics (High Ceiling)

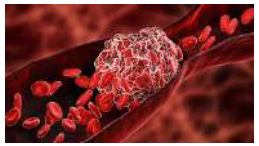
NKDA stands for No Known Drug Allergies

- works at the thick ascending limb of the loop of Henle
- are highly efficacious, and for this reason, they sometimes are called *high-ceiling diuretics.*
- Furosemide and bumetanide contain a sulfonamide moiety.
- Ethacrynic acid is a phenoxyacetic acid derivative and torsemide is a sulfonylurea
- loop diuretics increase in the urinary excretion of Na^+ and Cl^- profoundly, also K_+
- also results in marked increases in the excretion of Ca^{2+} and Mg^{2+}.

Table 28-4. Inhibitors of Na^+-K^+-$2Cl^-$ Symport (Loop Diuretics, High-Ceiling Diuretics)

DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	$T_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Furosemide (LASIX)		1	~60%	~1.5	~65% R, ~ 35% M*
Bumetanide (BUMEX)		40	~80%	~0.8	~62% R, ~38% M
Ethacrynic acid (EDECRIN)		0.7	~100%	~1	~67% R, ~33% M
Torsemide (DEMADEX)		3	~80%	~3.5	~20% R, ~80% M
Axosemide*		1	~12%	~2.5	~27% R, 63% M

- **Adverse Effects :**
  - abnormalities of fluid and electrolyte balance
  - Hyponatremia ↓ Na^+
  - Hypotension
  - thromboembolic episodes — condition that occurs when a blood clot forms in a vein.



  - circulatory collapse
  - increased urinary excretion of K^+ and H^+, causing a hypochloremic alkalosis
  - Hypokalemia ↓ K^+
  - Hypomagnesemia ↓ Mg^+
  - Hypocalcemia ↓ Ca^+
  - Ototoxicity
  - extra adverse effect (بالأذن الدوخة)
    - Hyperuricemia → gouts
    - Hyperglycemia

- Contraindications to the use of loop diuretics:

❖hypersensitivity to sulfonamides

❖Anuria

- Drug interactions:

➢Aminoglycosides → Ca^{+}

➢Anticoagulants

➢digitalis glycosides (increased digitalis-induced arrhythmias),

➢propranolol (increased plasma levels of propranolol)

➢Sulfonylureas

➢NSAIDs ⇝ ↑BP

Therapeutic Uses

- Acute pulmonary edema
- chronic congestive heart failure
- edema and ascites of liver cirrhosis
- HTN (not first choice) however in ER

vasodilation ↓ reduce periphral resistance

THIAZIDE AND THIAZIDELIKE DIURETICS

- Sulfonamides, derivatives of benzothiadiazine
- Drugs that are pharmacologically similar to thiazide diuretics but are not thiazides were developed and are called *thiazidelike diuretics.*

structure في

- inhibit NaCl transport in the **DCT**

long half-life

- the proximal tubule may represent a secondary site of action
- increase Na^+ and Cl^- excretion

Decrease the urinary excretion of ca .

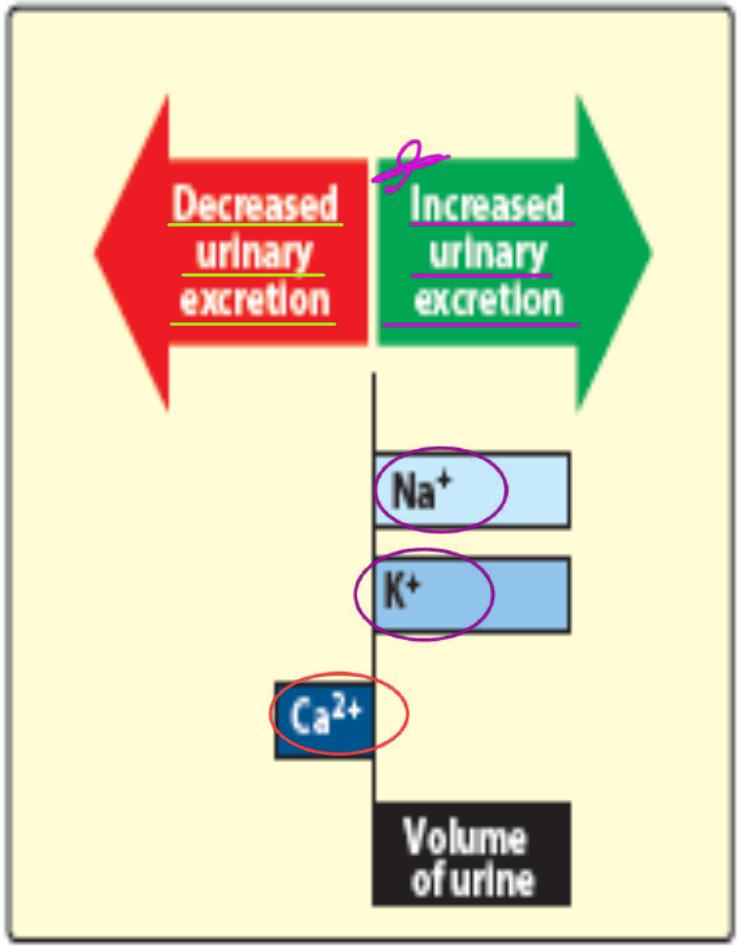


Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.

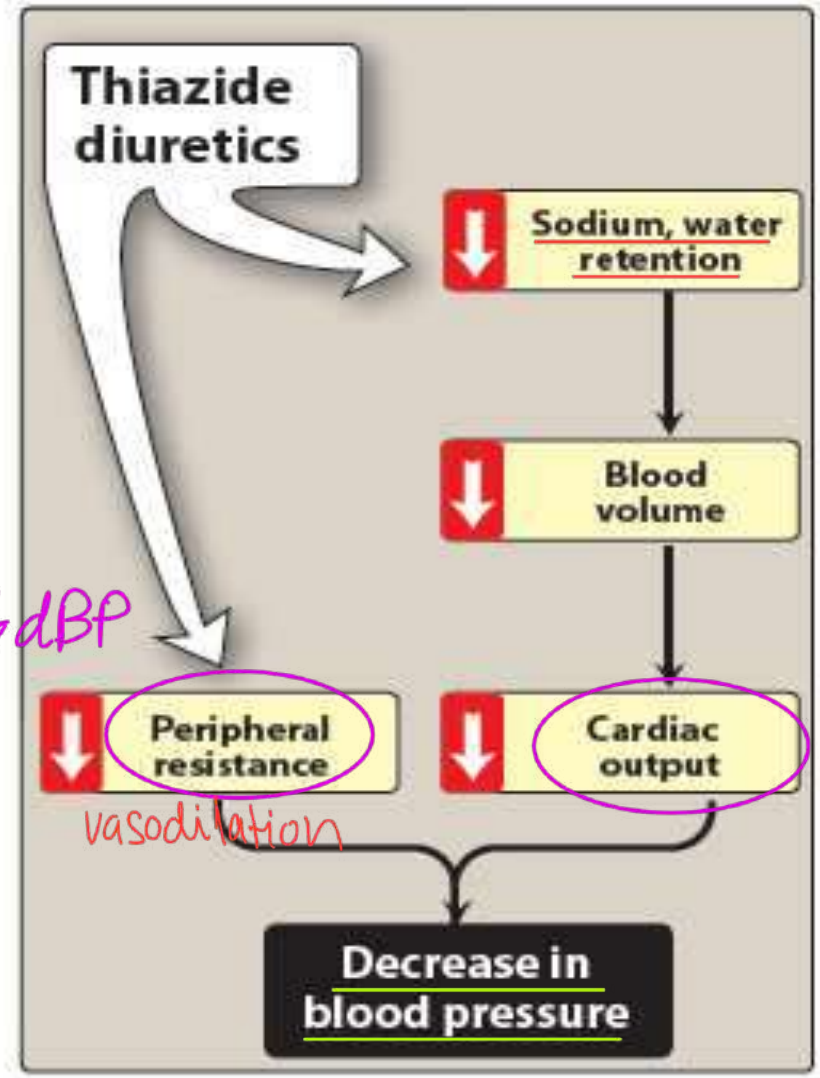


Figure 19.8
Actions of thiazide diuretics.

- thiazides are only moderately efficacious, because approximately 90% of the filtered Na^+ load is reabsorbed before reaching the DCT
- increase the excretion of K^+

Thiazide core structure

Adverse effects :

- extracellular volume depletion
- Hypotension
- hypokalemia ↓K
- hyponatremia ↓Na
- hypochloremia ↓Cl
- metabolic alkalosis
- Hypomagnesemia ↓Mg^{+}
- hypercalcemia ↑Ca
- hyperuricemia

hyperglycemia.
no ototoxicity.

Therapeutic Uses

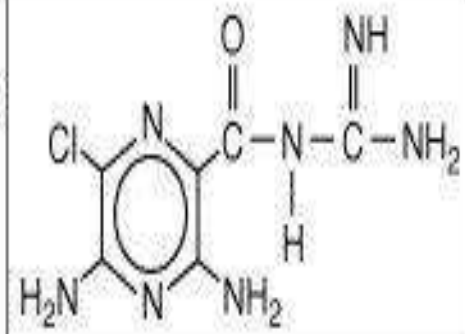
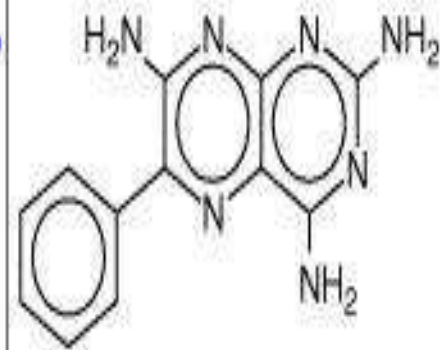
انتفاخ

- Edema : (CHF, RF, Liver cirrhosis)
- Moderate HTN either alone or in combination with other antihypertensive drugs
- A common dose for hypertension is 25 mg/day of hydrochlorothiazide or the dose equivalent of another thiazide.
- The ALLHAT study (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002) provides strong evidence that thiazide diuretics are the best initial therapy for uncomplicated hypertension, a conclusion endorsed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian *et al.2003)*

K^+-SPARING DIURETICS

- **Inhibitors of renal epithelial Na^+ channels**
- ***Triamterene*** and ***Amiloride*** are the only two drugs of this class in clinical use
- Both drugs cause small increases in NaCl excretion and usually are employed for their antikaliuretic actions to offset the effects of other diuretics that increase K^+ excretion
- **Triamterene** and **Amiloride**, along with Spironolactone (*see* next section), often are classified as *potassium (K^+)-sparing diuretics.*

Table 28-6. Inhibitors of Renal Epithelial Na^+ Channels (K^+-Sparing Diuretics)

DRUG	STRUCTURE	RELATIVE POTENCY	ORAL AVAILABILITY	$t_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Amiloride (DYRENIUM)		1	15-25%	~21	R
Triamterene (MIDAMOR)		0.1	~50%	~4.2	M

Abbreviations: R, renal excretion of intact drug; M, metabolism; however, triamterene is transformed into an active metabolite that is excreted in the urine

Adverse Effects

- The most dangerous adverse effect of Na^+-channel inhibitors is hyperkalemia, therefore contraindicated:
  - ❖ with NSAIDs
  - ❖With K supplement, or ACEIs,
- nausea, vomiting, diarrhea, and headache
- CNS, gastrointestinal, musculoskeletal, dermatological

ممنوع يتعطى مع ACE-I أو ARBs
برضه مع أي أشي برفع البوتاسيوم K
مثل: الموز ، السمك ، التين ، الأفوكادو
والفواكه المجففة خصوصًا الزبيب
وحتى السالمون.

Chest pain , palpitation irregular heart beat. (another side effect)

Therapeutic Uses

- seldom are used as sole agents
- major utility is in *combination* with other diuretics
- augments the diuretic and antihypertensive response to thiazide and loop diuretics (also decreases incidence of hypokalemia associated with loop andthiazide)

ALDOSTERONE ANTAGONISTS, K^+-SPARING DIURETICS

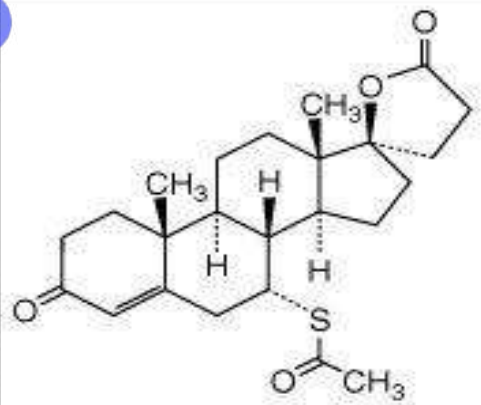
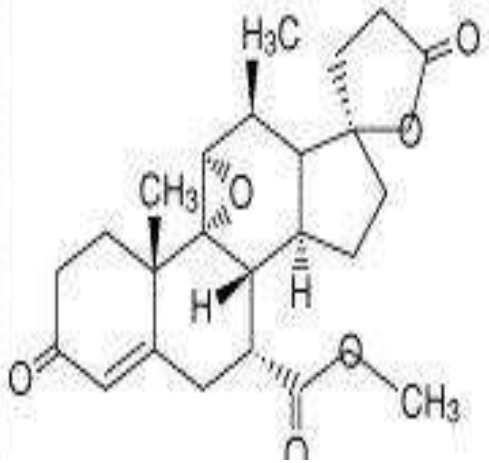
هاد النوع من الdiuretic مكنيا مايس استخدم مع ACEI لأنهم الاثنين بعملوا hyperkalemia.

- **antagonists of mineralocorticoid receptors**
- Mineralocorticoids cause retention of salt and water and increase the excretion of K^+ and H^+ by binding to specific mineralocorticoid receptors
- spirolactones block the effects of mineralocorticoids; this finding led to the synthesis of specific antagonists for the mineralocorticoid receptor (MR).
- two MR antagonists are available :
- *spironolactone* (a 17-spirolactone) and *eplerenone*

وظيفتهم يعملوا water و Na^+ الـ reabsorption و يعملوا H^+ و K^+ الـ excretion وعبا أني بدي دواء أزيد من الـ diuresis و لازم أزيد H^+ و K^+ reabsorption/Na^+ مع water excretion من عن طريق أني أعطي MR antagonist بهاي بالتالي واحد من الأشياء اللي رح يقص منك هي acidosis.

- Spironalactone acts on the distal convuluted tubules and the collecting duct
- Drugs such as spironolactone and eplerenone competitively inhibit the binding of aldosterone to the MR
- They increase excretion of Na and water, also enhance K and H retention.

Since spironolactone and eplerenone block the biological effects of aldosterone, these agents also are referred to as *aldosterone antagonists*

DRUG	STRUCTURE	ORAL AVAILABILITY	t 1/2 (HOURS)	ROUTE OF ELIMINATION
Spironolactone (ALDACTONE)		~65%	~1.6	M
Eplerenone (INSPRA)		ID	~5	M

an increase in the amount of breast gland tissue in boys or men.

- Spironolactone has some affinity toward progesterone and androgen receptors and thereby induces side effects: as gynecomastia, impotence, and menstrual irregularities.
- An active metabolite of spironolactone, canrenone, has a half-life of approximately 16.5 hours, which prolongs the biological effects of spironolactone
- Owing to the 9,11-epoxide group, eplerenone has very low affinity for progesterone and androgen receptors (<1% and <0.1%, respectively) compared with spironolactone. (no side effect)

Adverse Effects

- may cause life-threatening hyperkalemia
- Salicylates may reduce the tubular secretion of canrenone and decrease the diuretic efficacy of spironolactone
- spironolactone may alter the clearance of digitalis glycosides
- gynecomastia, impotence, decreased libido, hirsutism, deepening of the voice

e.g.: Aspirin

excess hair most often noticeable around the mouth and chin. With hirsutism, extra hair growth often arises from excess male hormones (androgens)

هاد الدواء إذا انطى مع Asprine رح يعطي (spironolactone) الـ effect تبع كيف؟؟

يؤثر الـ Aspirin أو أي اسم spironolactone رح ينافس الـ salicylic acid secretion inside the proximal DCT فإذا في ماي رح يوصل الـ spironolactone فإذا في ماي رح يتحمل على spironolactone effect (Na+ reabsorption) & (K+ excretion)

Therapeutic Uses

- spironolactone often is coadministered with thiazide or loop diuretics in the treatment of edema and hypertension
- treatment of primary hyperaldosteronism → ورم بسبب زيادة في افراز الـaldosterone
- hepatic cirrhosis → spironlactone is drug of choise.
  تشمع الكبد
- heart failure

* واحد من الأعراض التي بتصير مع الأشخاص اللي معهم liver cirrhosis هو ascites والتي هي تجمع الـ fluid في منطقة البطن و jaundice وهذا التشمع رح يأثر على تصنيع الـclotting factor لأنه عشان أصنعها في حاجة للـ vitamine K ومسؤول عن هاد الإشي هو الـliver بالتالي إذا ما تصنع عندي clotting factor رح يصير عندي تميع عالي بالدم وهاد الإشي رح الشخص ينزف لحتى يموت لأنه ما عندي عوامل تخثر ويصير عنده اشي اسمه epigastric varesis (دوالي في المريء) ويصير عنده "ascites".
* عاأنه صار عنده تجمع السوائل ف لازم أعطيه diuritic قوي هو المفروض أعطيه loop لأنه أقوى ولكن في حالة الـ hepatic cirrhosis الأفضل أعطيه spironolactone في حالة ascities.

INHIBITORS OF CARBONIC ANHYDRASE

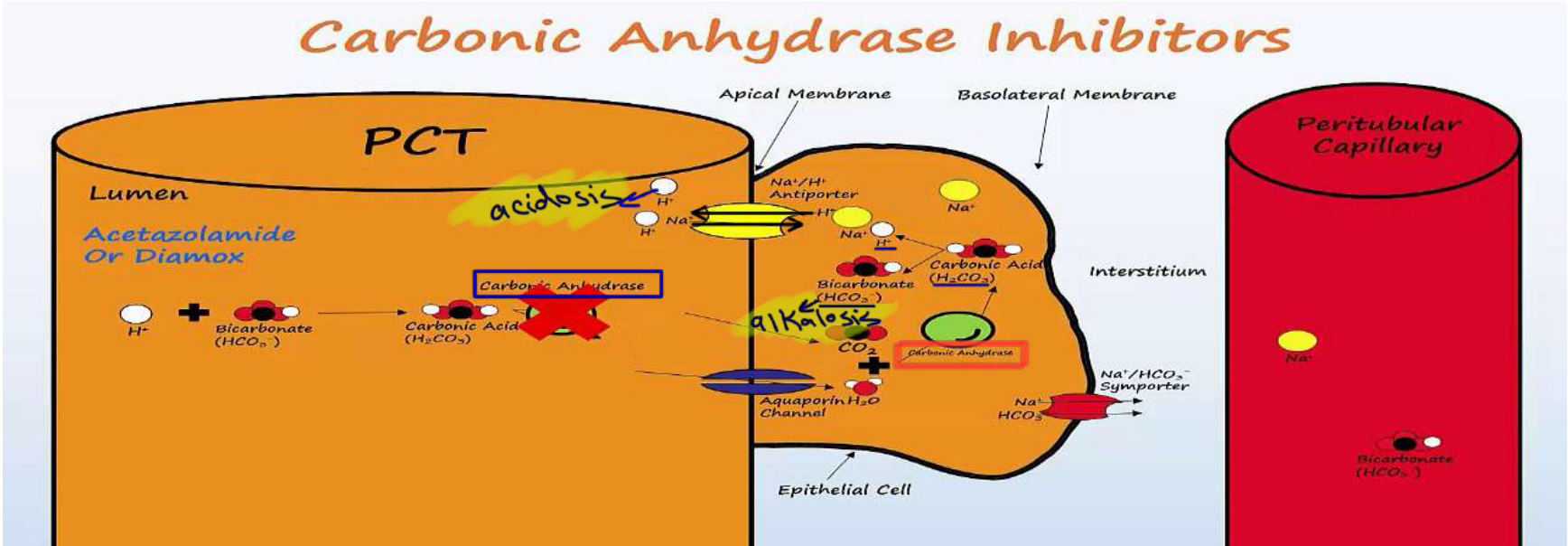
glucoma / mountain sikness

- *Acetazolamide* is the prototype of a class of agents
- Proximal tubular epithelial cells are richly endowed with carbonic anhydrase
- Carbonic anhydrase plays a key role in $NaHCO_3$ reabsorption and acid secretion.
- In the lumen, H^+ reacts with filtered HCO_3^- to form H_2CO_3, which decomposes rapidly to CO_2 and water in the presence of carbonic anhydrase (thousands of times) ↓urine alkalosis ↓blood acidosis.

- Carbonic anhydrase inhibitors potently inhibit both the membrane-bound and cytoplasmic forms of carbonic anhydrase, resulting in nearly complete abolition of $NaHCO_3$ reabsorption in the proximal tubule.

الطاءه

- Inhibition of carbonic anhydrase results in more alkaline urine (more HCO3 in urine)



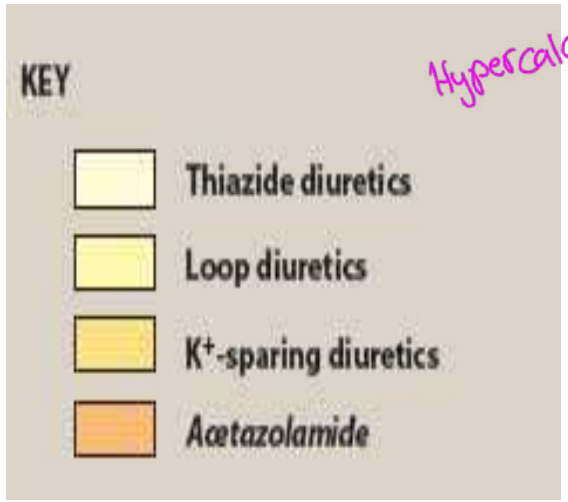
Adverse Effects

- Mainly well tolerated
- may cause bone marrow depression, skin toxicity,
- metabolic or respiratory acidosis

Therapeutic Uses

- Seldom used in clinical practice for HTN
- open-angle glaucoma (major indication) topically as eye drops

↓ mountain sickness



Na^+ excretion — Hyponatremia

Thiazide
loop
K+sparing
Aceta

K^+ excretion — Hypokalemia

Thiazied
loop
hypoKalemia
K+sparing
hyperKalemia
Aceta

Ca^{2+} excretion — Hypocalcemia

Hypercalcemia
Thiazide
loop
K+sparing
Aceta
hypocalcemia.

Volume of urine

Thiazide
loop
K+ sparing
AcetaZolamide.

OSMOTIC DIURETICS

- relatively inert pharmacologically.
- administered in large enough doses to increase significantly the osmolality of plasma and tubular fluid
- four currently available osmotic diuretics :
  - *Glycerin*
  - *isosorbide*
  - *mannitol*
  - *urea*

Mechanism and Site of Action

- Major site of action of osmotic diuretics is the loop of Henle.

✓ extracting water from intracellular compartments

✓ expand the extracellular fluid volume

✓ decrease blood viscosity

✓ inhibit renin release

لأنه قل عندي blood volume

Renal blood flow

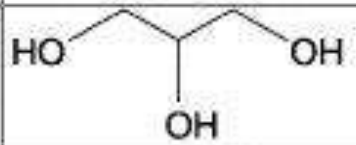
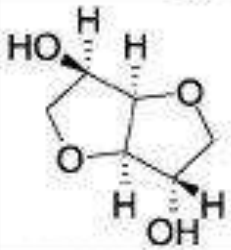
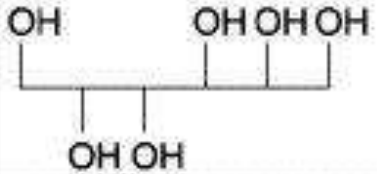
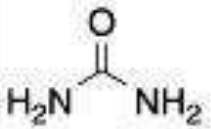
✓ These effects increase RBF

✓ increase in renal medullary blood flow

✓ removes NaCl and urea from the renal medulla

- Osmotic diuretics increase the urinary excretion of nearly all electrolytes, including Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, and phosphate.

Table 28-3. Osmotic Diuretics

DRUG	STRUCTURE	ORAL AVAILABILITY	$T_{1/2}$ (HOURS)	ROUTE OF ELIMINATION
Glycerin (OSMOGLYN)		Orally active	0.5–0.75	~80% M ~20% U
Isosorbide (ISMOTIC)		Orally active	5–9.5	R
Mannitol (OSMITROL)		Negligible	0.25–1.7*	~80% R ~20% M + B
Urea (UREAPHIL)		Negligible	ID	R

Adverse Effects

- In patients with heart failure or pulmonary congestion, they may cause frank pulmonary edema (since there is expantion in extracellular fluid volume)
- Hyponatremia
- Dehydration
- elevation of blood ammonia levels

Therapeutic Uses

- osmotic diuretics extract water from the eye and brain
- reduce cerebral edema
- In glucoma

+ acute renal failure.

OTHER VASODILATORS

α-ADRENOCEPTOR ANTAGONISTS

There are two main types of α-adrenoceptor, α1- and α2. α1-Adrenoceptor antagonists lower blood pressure

Phenoxybenzamine irreversibly alkylates α-receptors. It is uniquely valuable in preparing patients with phaeochromocytoma for surgery, but has no place in the management of essential hypertension. **Prazosin is a selective α1-blocker, but** its use is limited by severe postural hypotension, especially following the first dose. It has a short elimination half-life.

يعني راح أعطيه كبير

lipophilc / appeare in feces

Doxazosin is closely related to prazosin, but is longer lasting, permitting once daily use and causing fewer problems with first-dose hypotension. It did not compare well with diuretic, Ca2 antagonist or ACEI as first-line agent in ALLHAT, but is useful as add-on treatment in patients with resistant hypertension. It is given last thing at night.

Doxazosin improves symptoms of bladder outflow tract obstruction, and is useful in men with mild symptoms from benign prostatic hypertrophy

Mechanism of action

Noradrenaline activates α1-receptors on vascular smooth muscle, causing tonic vasoconstriction. α1-Antagonists cause vasodilatation by blocking this tonic action of **noradrenaline**

Adverse effects

TPN stands for Total Parenteral Nutrition

• First-dose hypotension and postural hypotension are adverse effects.

• Nasal stuffiness, headache, dry mouth and pruritus have been reported, but are relatively infrequent.

• α-Blockers can cause urinary incontinence, especially in women with pre-existing pelvic pathology.

Doxazosin has an elimination half-life of approximately 10–12 hours and provides acceptably smooth 24-hour control if used once daily

Table 28.3: Additional antihypertensive drugs used in special situations

Drug	Mechanism of action	Uses	Side-effects/limitations
Minoxidil	Minoxidil sulphate (active metabolite) is a K^+-channel activator	Very severe hypertension that is resistant to other drugs	Fluid retention; reflex tachycardia; hirsutism; coarsening of facial appearance. Must be used in combination with other drugs (usually a loop diuretic and β-antagonist)
Nitroprusside	Breaks down chemically to NO, which activates guanylyl cyclase in vascular smooth muscle	Given by intravenous infusion in intensive care unit for control of malignant hypertension	Short term IV use only: prolonged use causes cyanide toxicity (monitor plasma thiocyanate); sensitive to light; close monitoring to avoid hypotension is essential
Hydralazine	Direct action on vascular smooth muscle; biochemical mechanism not understood	Previously used in 'stepped-care' approach to severe hypertension: β-antagonist in combination with diuretic. Retains a place in severe hypertension during pregnancy	Headache; flushing; tachycardia; fluid retention. Long-term high-dose use causes systemic lupus-like syndrome in susceptible individuals
α-Methyldopa	Taken up by noradrenergic nerve terminals and converted to α-methylnoradrenaline, which is released as a false transmitter. This acts centrally as an α_2-agonist and reduces sympathetic outflow	Hypertension during pregnancy. Occasionally useful in patients who cannot tolerate other drugs	Drowsiness (common); depression; hepatitis; immune haemolytic anaemia; drug fever