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).

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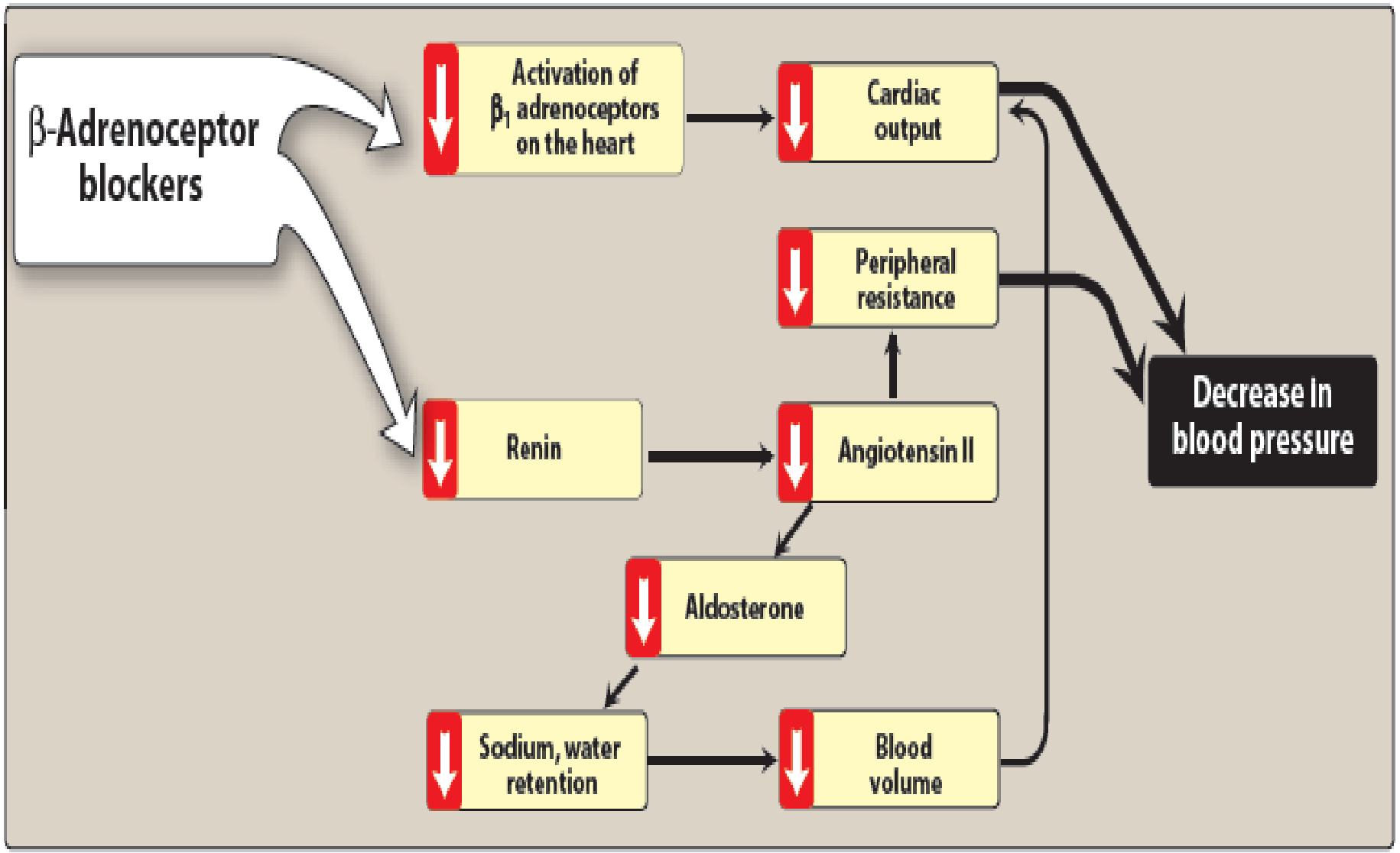
MOA


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

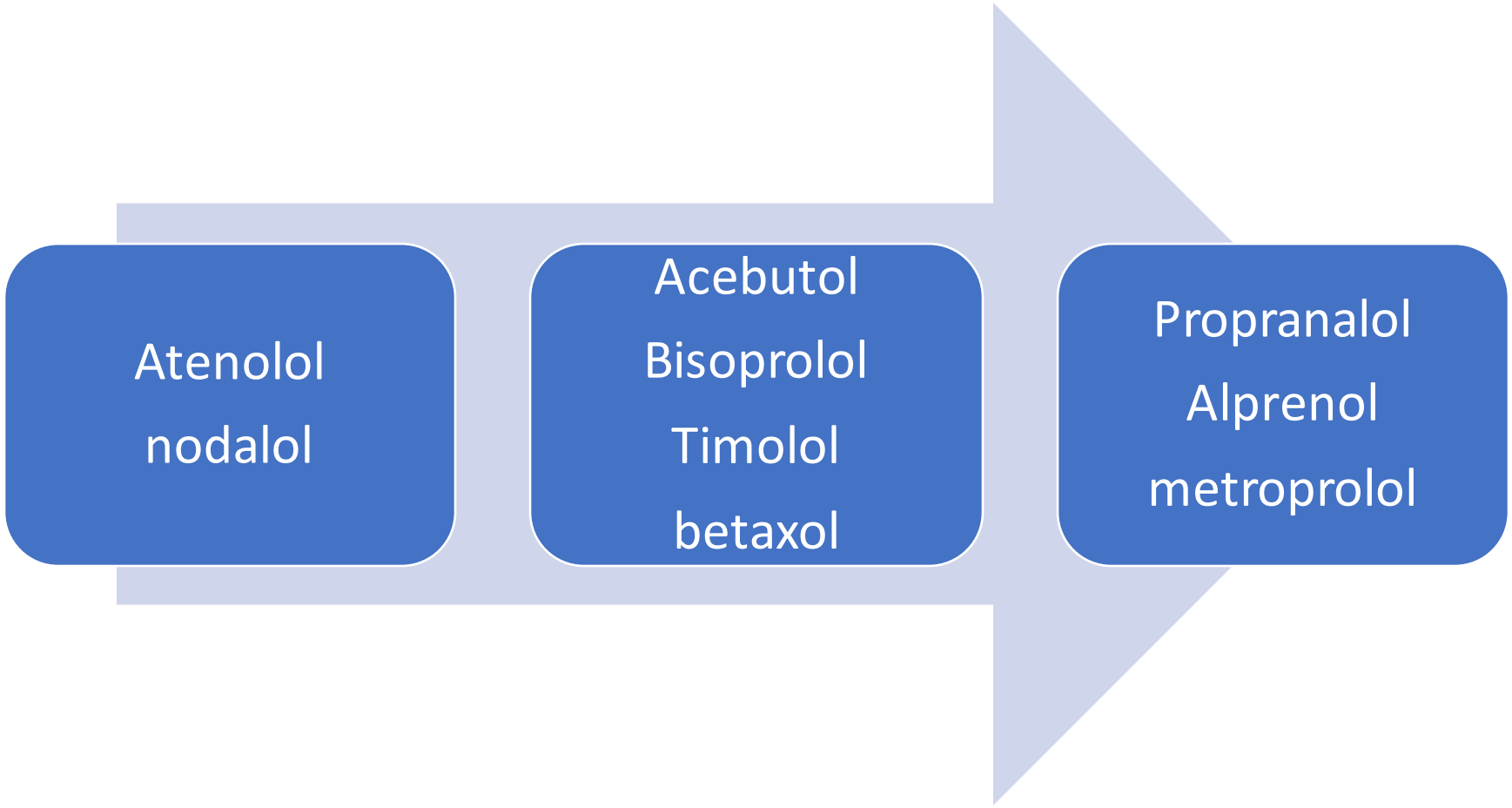
- Given intravenously in emergencies (Esmolol)

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

- 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.

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)

Contraindications :

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

Adverse effects and contraindications :

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

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

• *Hypoglycaemia*

• *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 !!!

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.

➢ Calcium-channel blockers therefore relax arteriolar smooth muscle, reduce peripheral vascular resistance 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.

- **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)

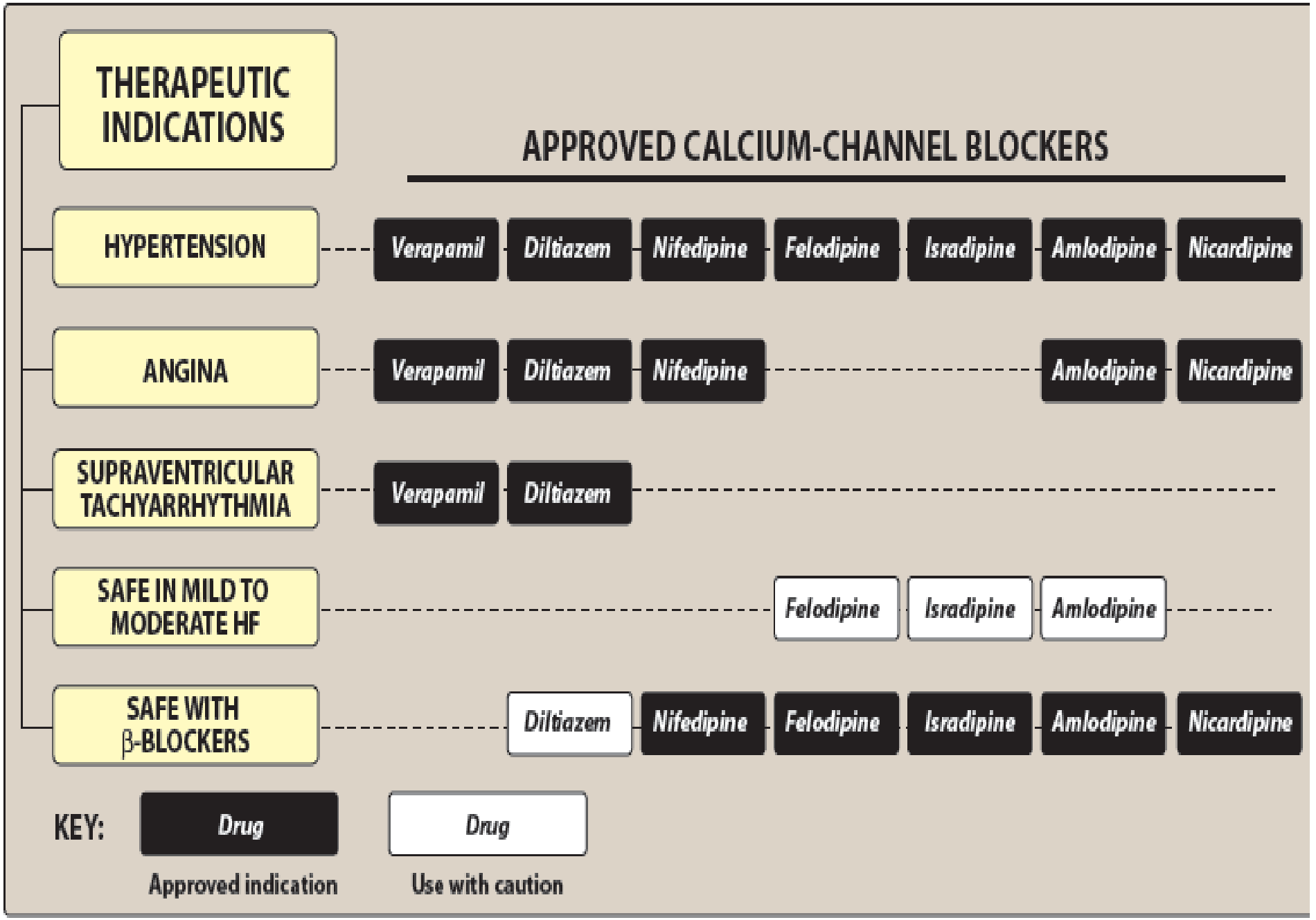
- Ankle swelling (oedema) is common .
- The negative inotropic effect of **verapamil exacerbates** cardiac failure.
- Constipation is common with **verapamil.**

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


THERAPEUTIC INDICATIONS
APPROVED CALCIUM-CHANNEL BLOCKERS
HYPERTENSION
Verapamil
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
ANGINA
Verapamil
Diltiazem
Nifedipine
Amlodipine
Nicardipine
SUPRAVENTRICULAR TACHYARRHYTHMIA
Verapamil
Diltiazem
SAFE IN MILD TO MODERATE HF
Felodipine
Isradipine
Amlodipine
SAFE WITH β-BLOCKERS
Diltiazem
Nifedipine
Felodipine
Isradipine
Amlodipine
Nicardipine
KEY:
Drug
Approved indication
Drug
Use with caution

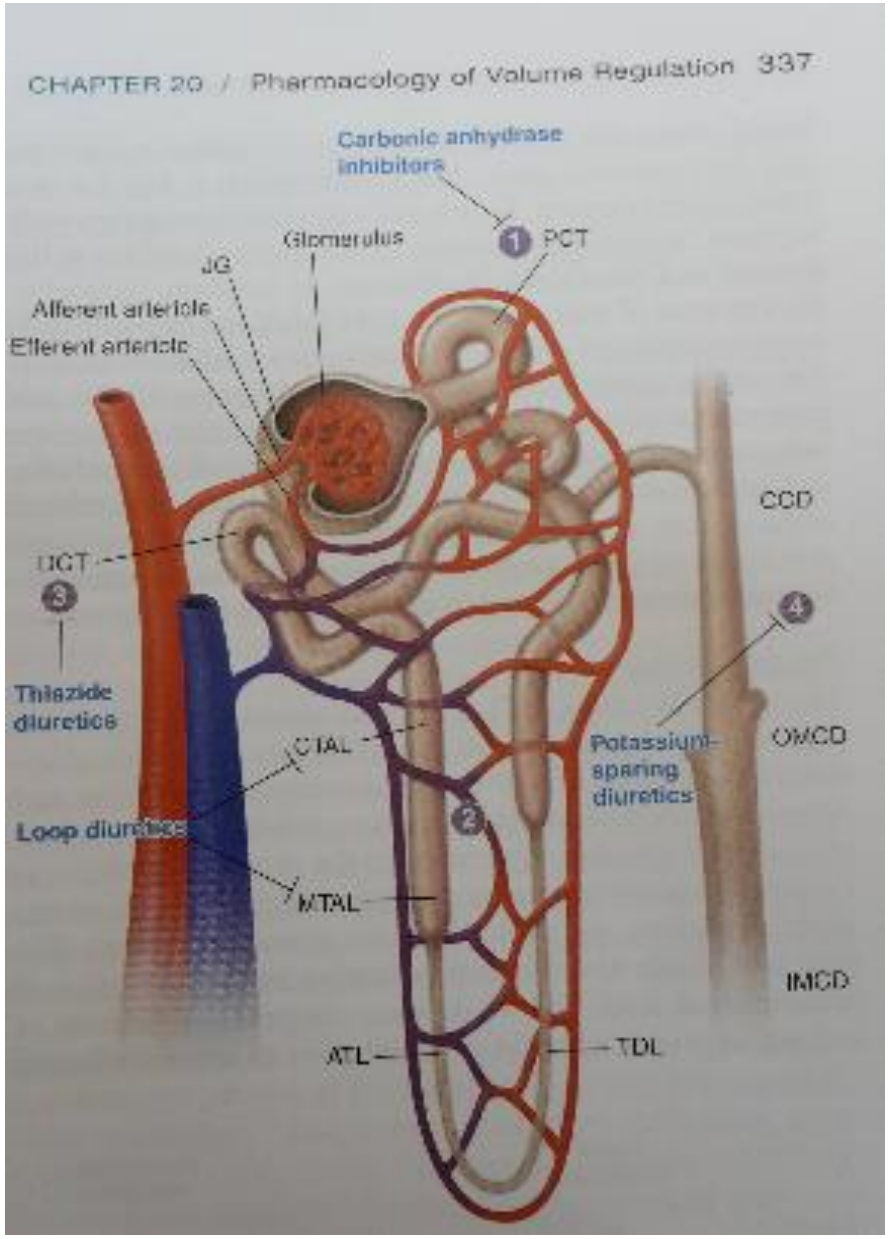
D DRUGS
DIURETICS

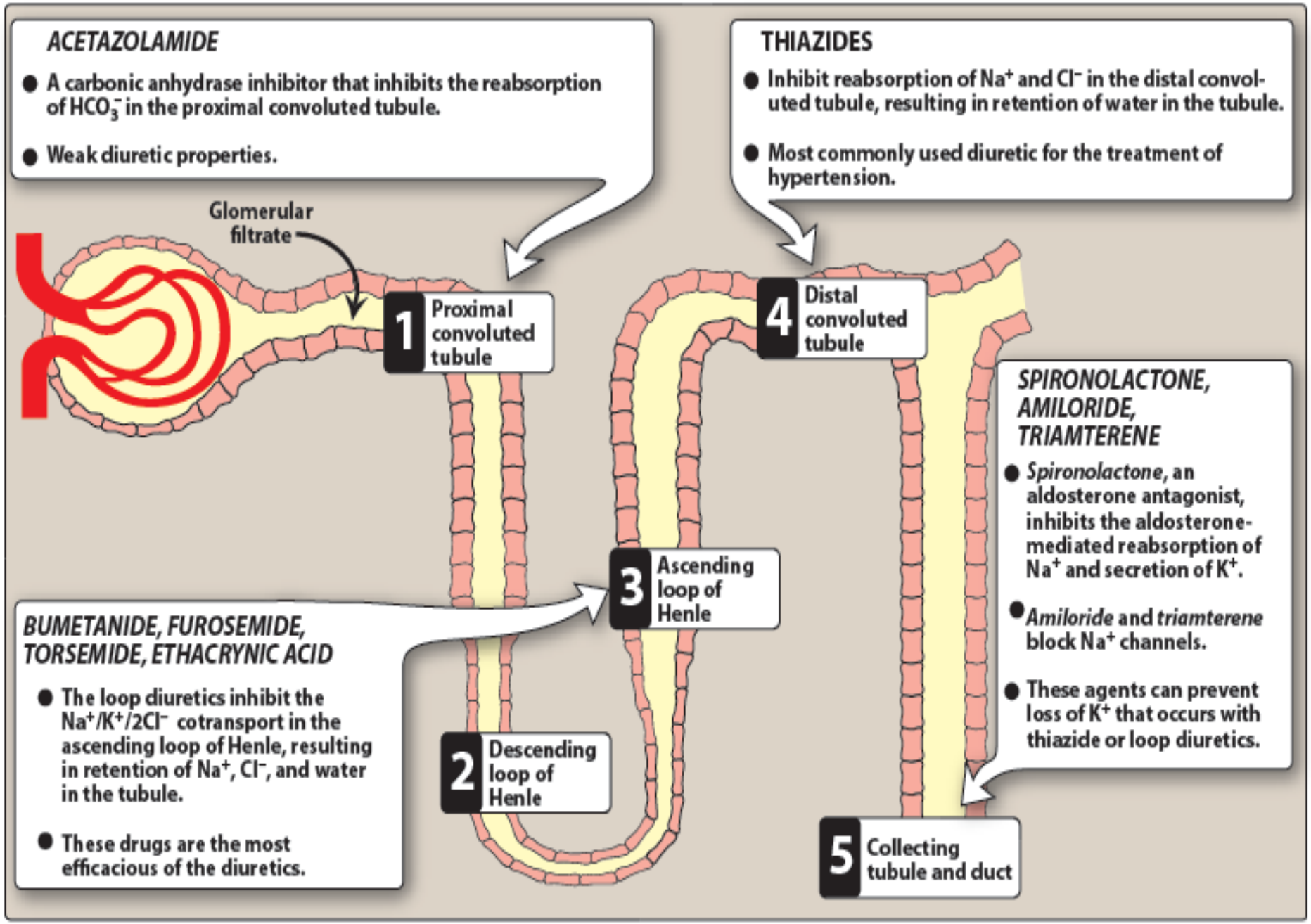
PRINCIPLES OF DIURETIC ACTION

- 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.
THIAZIDES
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.

Solute transport and reabsorption sites

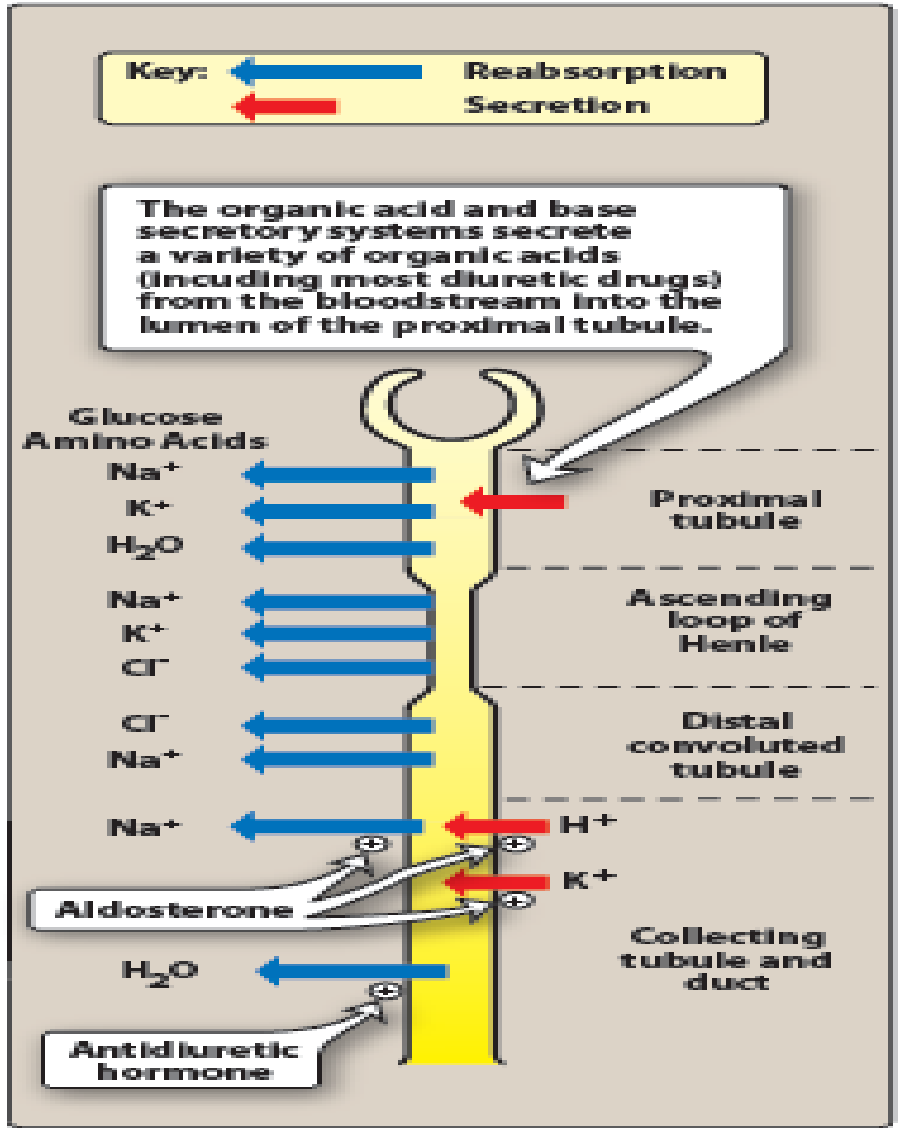
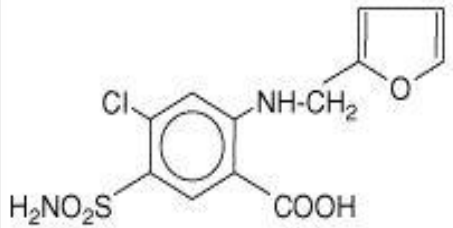
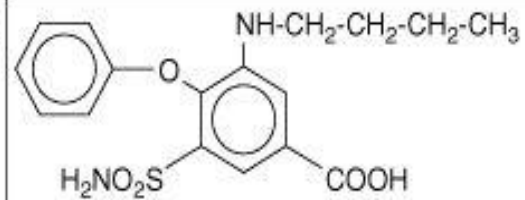
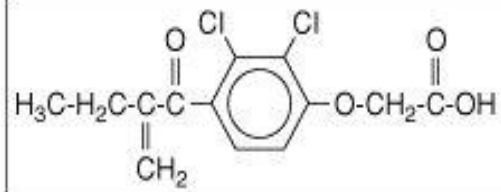
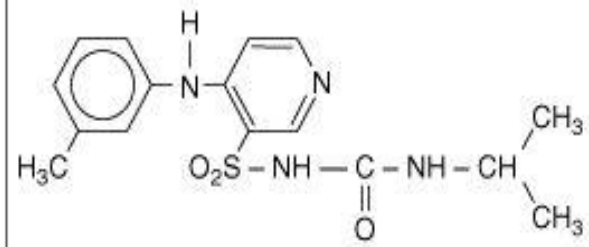
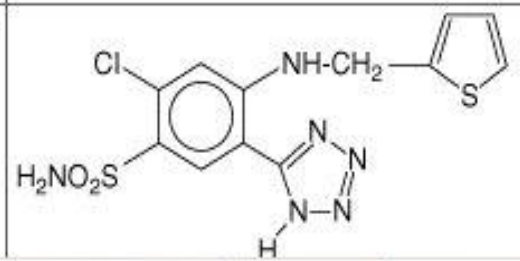


Figure 22.3
Sites of transport of solutes and water along the nephron.

Loop Diuretics (High Ceiling)

- 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
  - Hypotension
  - thromboembolic episodes
  - circulatory collapse
  - increased urinary excretion of K^+ and H^+, causing a hypochloremic alkalosis
  - Hypokalemia
  - Hypomagnesemia
  - Hypocalcemia
  - Ototoxicity

- Contraindications to the use of loop diuretics :

❖hypersensitivity to sulfonamides

❖Anuria

- Drug interactions :

➢Aminoglycosides

➢Anticoagulants

➢digitalis glycosides (increased digitalis-induced arrhythmias),

➢propranolol (increased plasma levels of propranolol)

➢Sulfonylureas

➢NSAIDs

Therapeutic Uses

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

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.*
- inhibit NaCl transport in the **DCT**
- the proximal tubule may represent a secondary site of action
- increase Na^+ and Cl^- excretion

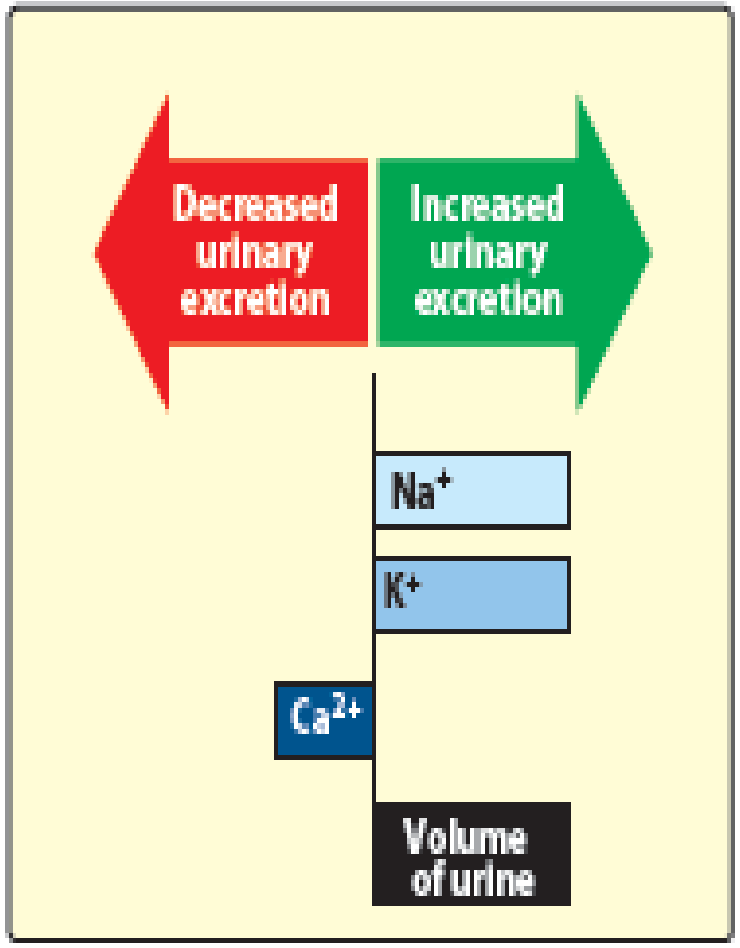


Figure 22.4
Relative changes in the composition of urine induced by thiazide diuretics.

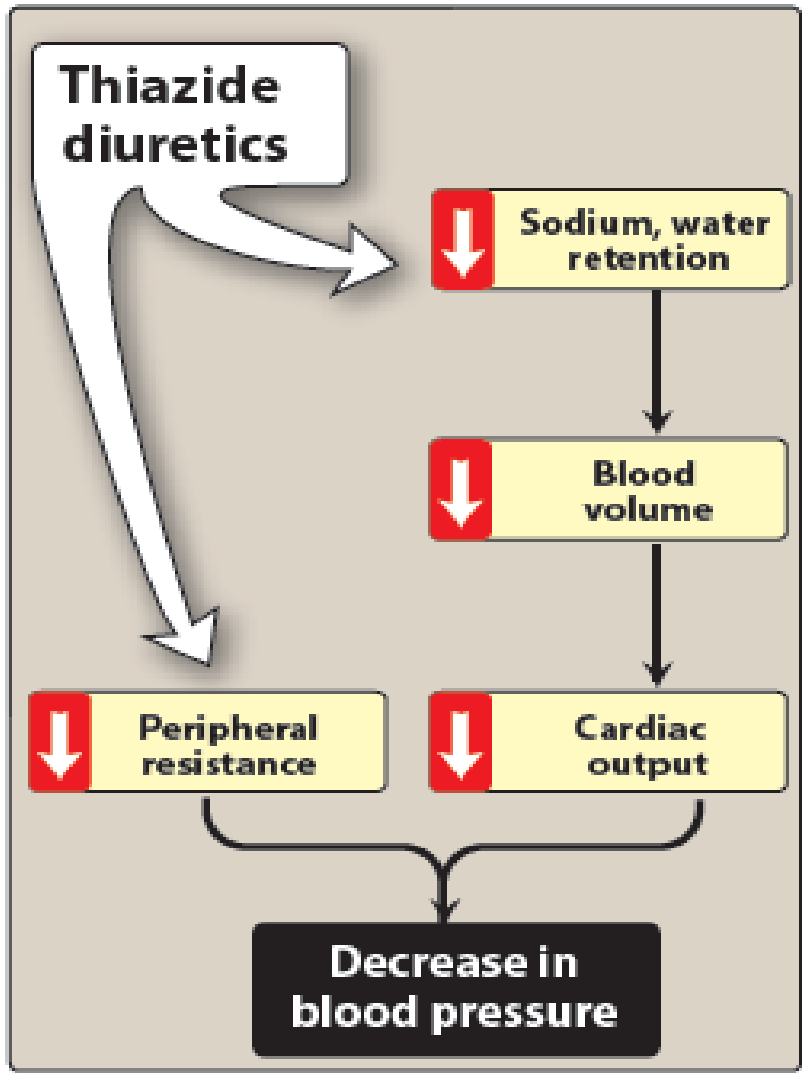
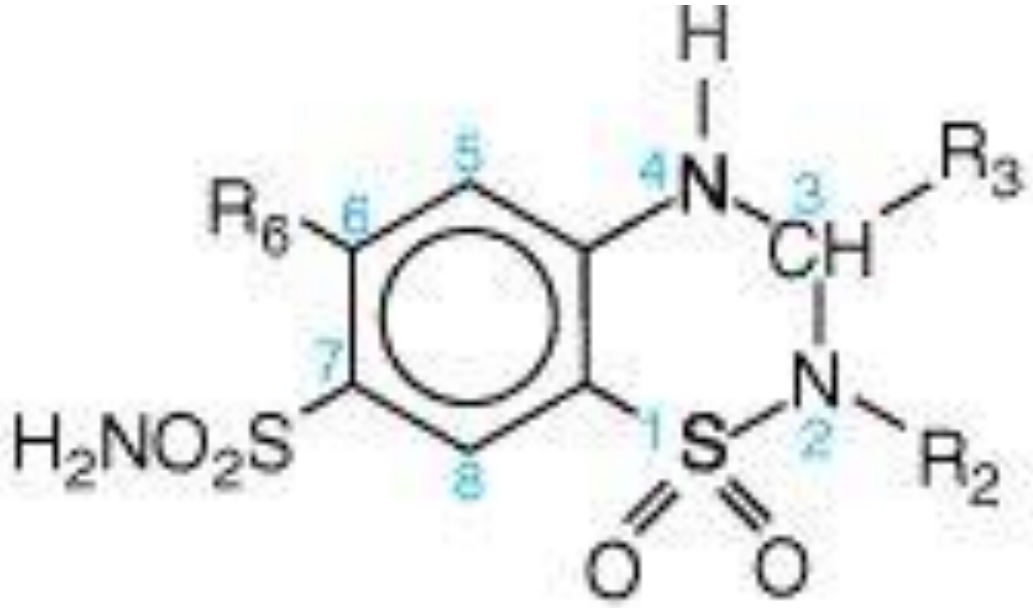


Figure 19.8
Actions of thiazide diuretics.

- 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
- hyponatremia
- hypochloremia
- metabolic alkalosis
- Hypomagnesemia
- hypercalcemia
- hyperuricemia

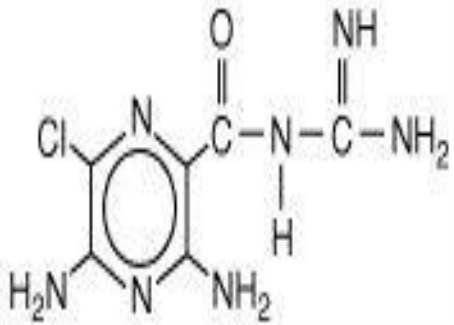
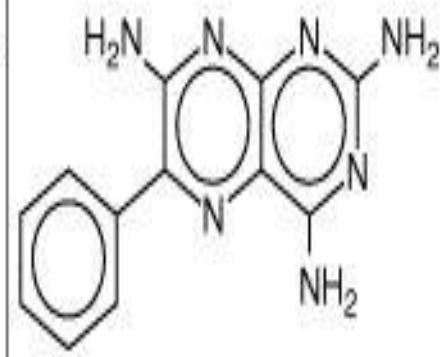
Therapeutic Uses

- 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

Therapeutic Uses

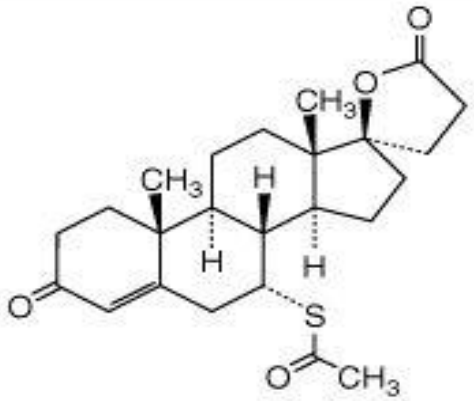
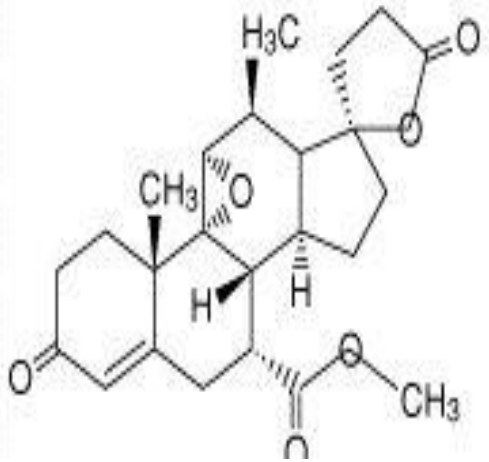
- seldom are used as sole agents
- major utility is in *combination* with other diuretics
- augments the diuretic and antihypertensive response to thiazide and loop diuretics (also decreases incidence of hypokalemia associated with loop andthiazide)

ALDOSTERONE ANTAGONISTS, K^+-SPARING DIURETICS

- **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*

- 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

- 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.

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

Therapeutic Uses

- spironolactone often is coadministered with thiazide or loop diuretics in the treatment of edema and hypertension
- treatment of primary hyperaldosteronism
- hepatic cirrhosis
- heart failure

INHIBITORS OF CARBONIC ANHYDRASE

- *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)

- 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.

- 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

OSMOTIC DIURETICS

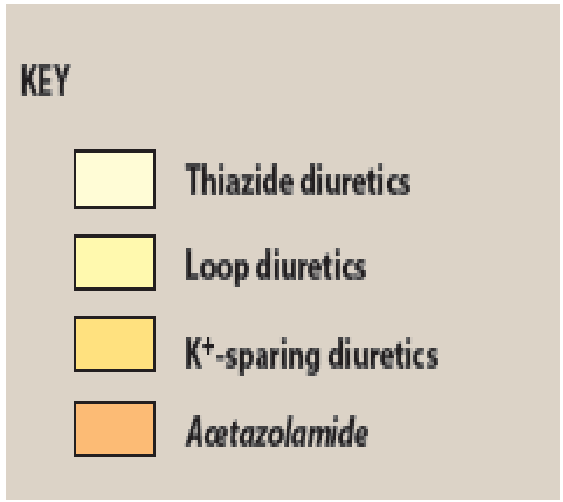
- relatively inert pharmacologically
- administered in large enough doses to increase significantly the osmolality of plasma and tubular fluid
- four currently available osmotic diuretics :

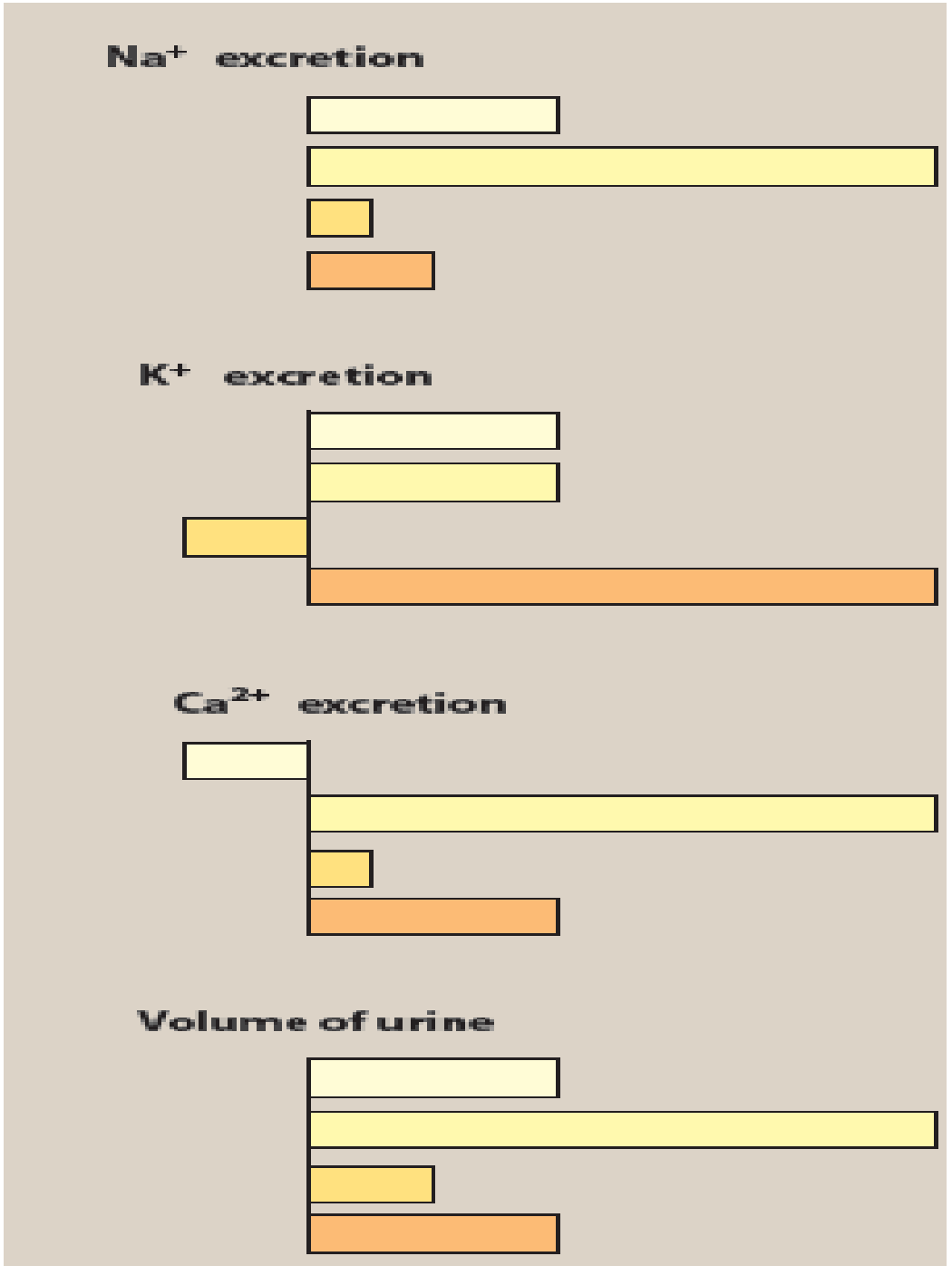
➢ *Glycerin*

➢ *isosorbide*

➢ *mannitol*

➢ *urea*


KEY
Thiazide diuretics
Loop diuretics
K+-sparing diuretics
Acetazolamide


Na+ excretion
K+ excretion
Ca2+ excretion
Volume of urine

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

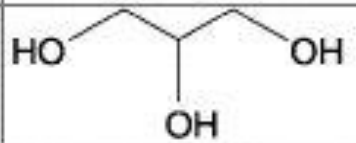
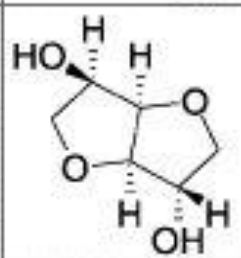
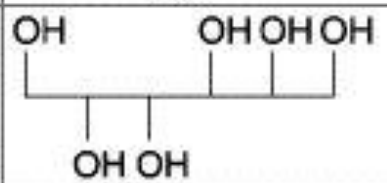
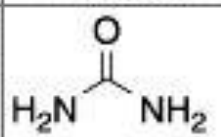
✓These effects increase RBF

✓ 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

*I[illegible]

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

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.

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 (Chapter 36), 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

• 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