Drugs for ischemic heart disease

Pál Riba, M.D., Ph.D

Department of Pharmacology and Pharmacotherapy, Semmelweis University

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Ischemic heart disease

Disturbance in the oxygene demand/supply of the heart due to the arteriosclerosis of the coronary arteries or to their pathological

Factors influencing the oxygene balance of the heart

- Wall stress (preload)
  - End-diastolic volume
  - End-diastolic pressure
  - Wall thickness
- Heart rate
- Contractility (strength of contraction)
- Afterload (arterioles, diastolic blood pressure)

Disturbance in the oxygene balance

- Icreased oxygene demand
  - Increasing preload(venoconstriction, RAAS activity – volume!)
  - Increasing heart rate and contractility (sympathetic activity)
  - Higher blood pressure
  - Chronically thickened heart wall
- Decreased oxygene supply
  - Increasing heart rate (decreased diastole time, decreased coronary flow)
  - Coronary disease (arteriosclerosis)

Definition and types of angina pectoris

- Chest pain due to the insufficient oxygene supply to the heart (pressure-like pain)
- Types:
  - Chronic stable angina = effort angina (strictures and bad perfusion due to coronary sclerosis)
  - Unstable angina (coronary plaque thrombosis caused acute coronary occlusion = acute infarction risk!!!)
  - Prinzmetal angina (coronary spasm)

Drugs for chronic stable angina

- Nitrates (eg. nitroglycerin)
  - NO release, cGMP level ↑, blood vessels relax, preload ↓ due to venodilation, coronary dilation
- Beta-blockers
  - Only prophylactic, heart rate ↓, contractility ↓, longer diastole, weak RAAS inhibition
- Ca^{++}-channel (L-type) blockers
  - Mainly decreased afterload and coronary dilation
- Improving energy consumptions (trimetazidine)
  - Inhibition of fatty acid oxidation, ATP production ↑, citrate cycle loading ↑ due to increased glycolysis
- Funny channel inhibitor
  - ivabradine

Treatment of unstable angina

- Acute coronary intervention (stent)
- Inhibition of platelet aggregation (acetylsalicylic acid or clopidogrel)
- For prevention: platelet aggregation inhibitors, ACE-inhibitors, drugs that decrease cholesterol level (these are also used in stable angina)

Treatment of coronary spasm

- Ca^{++}-channel blockers
- Beta-blockers are forbidden!!!!

Nitrates and their side effects

- Nitroglycerin (both to treat or prevent acute angina attack), isosorbid-mononitrate, molsidomin
- Side effects:
  - Throbbing headache
  - Dizziness,
  - Drop in blood pressure (hypotension),
  - reflex tachycardia,
  - flushing,
  - nausea,
  - Numbing tongue,
  - methemoglobinemia

Beta blockers and their side effects

- Propranolol, Metoprolol, Bisoprolol, Carvedilol (this is a mixed alfa1-beta antagonist)
- Side effects
  - Bradycardia
  - AV-block
  - Cardiac decompensation
  - Bronchconstriction (CAVE asthma bronchiale!!!)
  - Peripheral vasoconstriction (cold feet and hands, except carvedilol)
  - Hypercholesterolemia
  - Impotence
  - Prolonged hypoglycemia

Ca^{++}-channel blockers and their side effects

- Verapamil and diltiazem
  - Bradycardia
  - AV-block
  - Hypotension
- Dihydropiridines (eg. amlodipin)
  - Hypotension
  - Reflex tachycardia
  - Ankle edema
  - Constipation
  - Provoking angina attack

CONGESTIVE HEART FAILURE

Definition of heart failure

Decrease of cardiac output when it is unable to provide sufficient oxygenization and tissue perfusion of the peripheral organs.

Compensatory mechanisms

- Increased sympathetic tone
  - → increasing cardiac output
  - → increasing contractility
  - → increasing preload due to the decreasing venous capacitance
  - → Increasing activity of RAAS → aldosterone increases the circulating volume → increasing cardiac output
- Due to the increased preload
  - → higher stroke volume → more pronounced dilation → increasing contractility (Frank-Starling law)
- Chronic process → ventricular hypertrophy

Congestive heart failure:

- Compensatory mechanisms are unable to switch the heart to satisfy the increased demand → DECOMPENSATION
- The overstimulated compensatory mechanisms further impair the pumping function of the heart
- Aims:
  - To slow down the pathologically stimulated compensatory mechanisms
  - To support the heart with medicines

Drugs used in congestive heart failure

- ACE-inhibitors, AT_1-antagonists
  - To decrease afterload, to inhibit the remodelling process
- β-blockers
  - they inhibit the increased sympathetic activity
  - decrease the risk of mortality
- Diuretics
  - they decrease the preload
- Venodilators
  - they decrease the preload
- Positive inotropic drugs
  - Cardiac glycosides → for systolic type of heart failure (LVEF<40%)
  - Other positive inotropic drugs → for very severe heart failure

Drugs acting on the RAAS

- Renin antagoniss – aliskiren
  - Inhibition of angiotenzinogene-angiotenzin I conversion
- Angiotenzin-converting enzyme (ACE) blockers
  - Inhibition of angiotenzin I – angiotenzin II conversion
- Angiotenzin II receptor (AT_1) antagonists
  - Inhibit the actions of angiotenzin II in the vessels and adrenal cortex
- Aldosterone antagonists – spironolactone, eplerenone
  - Inhibit the effects of aldosterone in the kidney
- „0.” group: beta-receptor blockers
  - Inhibition of renin release

ACE-inhibitors and their effects I.

- There are at least 13 ACE-inhibitors marketed
  - captopril, lisinopril, enalapril, ramipril, perindopril, cilazapril, fosinopril, benazepril, spirapril, quinapril, trandolapril, zofenopril, moexipril
- 2 of them is active (captopril, lisinopril), the rest are prodrugs
  - Esterase enzymes convert them to active acids
- They inhibit the formation of angiotenzin II and the metabolism of bradykinin
- Main actions of angiotenzin II: aldoszteron secretion ↑, vasoconstriction, pathological remodelling of heart wall and blood vessels ➔ ACE-inhibitors inhibit all of these effects

ACE-inhibitors and their effects II.

- First choice drugs in congestive heart failure
- Other indications:
  - Hypertension, diabetic nephropathy, prevention of cardiovascular events, myocardial infarction
- Main side effects: dry cough (bradykinin), hyperkalemia!!!, acute renal failure, hypotension, angioneurotic edema, teratogenicity (2nd and 3rd trimester are absolute contraindication)
- RAAS inhibitors cannot be combined due to the higher risk of hyperkalemia

AT_1 antagonists and their effects

- Basically similar to ACE-inhibitors
  - losartan, valsartan, irbesartan, candesartan, olmesartan, telmisartan, eprosartan
- Indications:
  - Hypertension, congestive heart failure, diabetic nephropathy, myocardial infarction
- Main side effects: hyperkalemia!!!, acute renal failure, hypotension, teratogenicity (2nd and 3rd trimester are absolute contraindication)
- Dry cough is less common compared to ACE-inhibitors

Aldosterone antagonists and their effects

- Primarily diuretics, spironolactone is actually used like that
- Eplerenone is indicated in CHF, it has diuretic action
- Their diuretic ection is slow – for details see diuretics

Diuretics

See later

Vazodilators

- In CHF preload decrease is essential ➔ venodilators:
- Nitrates: nitroglicerin
  - Mechanism: NO release -> cGMP ↑-> smooth muscle relaxation
  - Indications: angina pectoris, hypertensive crisis, congestive heart failure
  - When given continuously very rapid tolerance develops against them – intermittent administraion
  - In CHF the acute condition of the patient is improving but they do not influence survival

Beta-blockers and congestive heart failure

- Theiretically they are illogical due to their negative inotropic effect BUT!!!
- In CHF sympathetic activity is pathologically higher
- Heart has higher catecholamine sensitivity ➔ high risks of arrythmia, furtehr increased by hypoxia ➔ beta-blockers may decreasse this risk
- Should be given slowly until decompensation signs appear
- metoprolol, bisoprolol, nebivolol, carvedilol

Positive inotropic drugs

- They strengthen the pump – stronger contractions
- Acute drugs:
  - Sympathomimetics:
    - $beta_1$ agonist: dobutamine, dopamine
    - alfa-beta1 agonist noradrenaline (norepinephrine)
  - cPDE-3 inhibitors:
    - Milrinone
  - Ca^{++}-sensitizers:
    - Levosimendan
- Chronic drugs: Cardiac glycosides

Using sympathomimetics in CHF

- Only in very severe decompensation:
  - NYHA IV grade
  - Cardiogenic shock
- Strong tachycardia ➔ arrhythmia!!!
- Tolerance to dobutamine
- Norepinephrine ➔ strong vasoconstrictor, diastolic pressure ↑, less tachycardia

cPDE-3 inhibitors

- Milrinone:
  - In case of dobutamine resistance, not used chronically due to its arrhythmogenic effect, may increase mortality rate
- Every Ca^{++}-level increasing drug is arrhythmogenic in the heart

Ca^{++}-sensitizers

- Levosimendan
  - Increases the Ca^{++} sensitivity of troponin-C, theoretically positive inotropic without increasing Ca^{++}- level
  - Indicated for NYHA IV grade
  - Less arrhythmogenic than the previous ones

Cardiac glycosides and their features I.

- Digoxin, digitoxin (deslanosid, acetyldigitoxin, strophantin, ouabain)
- Structure:
  - steroid core + unsaturated lactone ring connected to D ring = genin
  - Genin + sugar chain = glikoside
- Na^+/K^+-ATP-ase inhibitors → IC Na^+ increases → Na^+/Ca^{++} exchange slows down → IC Ca^{++} increases → more Ca^{++} is stored in SR → AP initiates higher Ca^{++} current → **positive inotropic effect**

Cardiac glycosides and their features II.

- Central vagus stimulating effect
  - → increasing parasympathetic tone in the heart → ACh through M_2 receptors opens a K^+ channel → hyperpolarization → sinus and AV nodes slow down → **bradycardia**
- Arrhythmogenic effect
  - Increasing bradycardia
  - Further slowing conduction → **AV-block**
  - Ca^{++} overload in the ventricular muscle cell → due to Ca^{++} fluctuation delayed after-depolarization → **ventricular extrasystole** → ventricular tachycardia, ventricular fibrillation
- Very common symptom
  - bardycardia + ventricular ES → **bigeminia**

Pharmacokinetics of cardiac glycosides

Digoxin	Property	Digitoxin
75%	Absorption	>90%
25%	Plasma protein binding	98%
0,5-1 hour	Onset time	3-6 hours
not metabolized	Metabolism	in the liver
Kidney	Excretion	Liver
36-40 hours	Half life	5-7 days!!!
1-1,5mg	Loading dose	0,8-1mg
0,25mg	Maintenance dose	0,07-0,1mg

Indications of cardiac glycosides

- Chronic congestive heart failure (NYHA III-IV)
- Atrial flutter, atrial fibrillation
- Rarely: supraventricular tachycardia

Contraindications of cardiac glycosides

- Hypertrophic cardiomyopathy
- Some forms of WPW-syndrome (digitalis stimulates the anterograde conduction, ventricular tachycardia may develop)
- AV-block
- Suspected digitalis intoxication
- Diastolic heart failure

Warnings, cardiac glycosides should be avoided

- Sinus bradycardia, sick sinus syndrome
- Concomitant use with other negative chronotropic agents (verapamil, diltiazem, amiodaron) $\rightarrow$ severe bradycardia
- Stages with increased digitalis sensitivity (eg. hypokalemia)
- Renal failure (digoxin)

Important interactions of cardiac glycosides

- Hypokalemia!!! → increases toxicity
  - Potassium wasting diuretics (loop diuretics, thiazides)
  - WHY? Cardiac glycosides bind to the potassium bindind site of Na^+/K^+-ATP-ase, they can be considered potassium antagonists (and vice versa)
- Hypercalcemia → increases toxicity
- Hypomagnesinemia → increases toxicity
  - ATP-ase enzymes require magnesium, when the pump works weaker, the inhibition may be more pronounced
- Hyperkalemia → decreases the effect and the toxicity
  - Potassium sparing diuretics (spironolactone, amilorid)
  - ACE-inhibitors, AT_1 antagonists → aldosterone effect decreases

Digitalis intoxication and its treatment

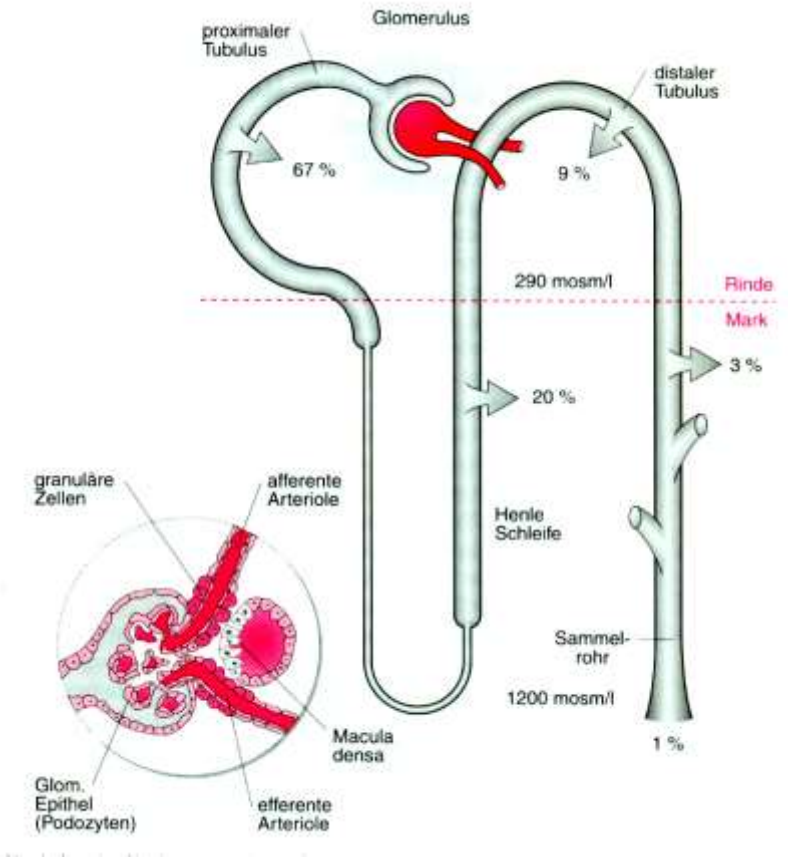
- Symptoms:
  - Extreme bradycardia, AV-block, bigeminia, ventricular tachycardia, ventricular fibrillation
  - ECG: ST-depression, T-inversion
  - Color vision disturbances (yellowish colors), blurred vision, photosensitivity
  - Headache, anxiety, nightmares, hallucinations
  - Nausea, abdominal pain
- Treatment
  - Digitalis binding antibody (mainly for suicide attempts)
  - Treating the electrolite disturbance
  - I/B type antiarrhythmic drugs (lidocaine, phenytoin)

DIURETICS

Definition

- Diuretics increase the rate of urine flow.
- The clinically relevant diuretics increase the Na excretion.
- Extrarenal “diuretics”: act outside the nephron (eg. caffeine, dopamine)
- Renal diuretics: they influence the nephron functions

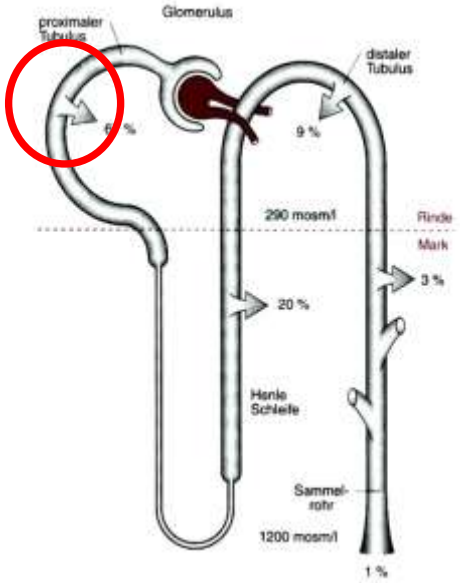
The nephron

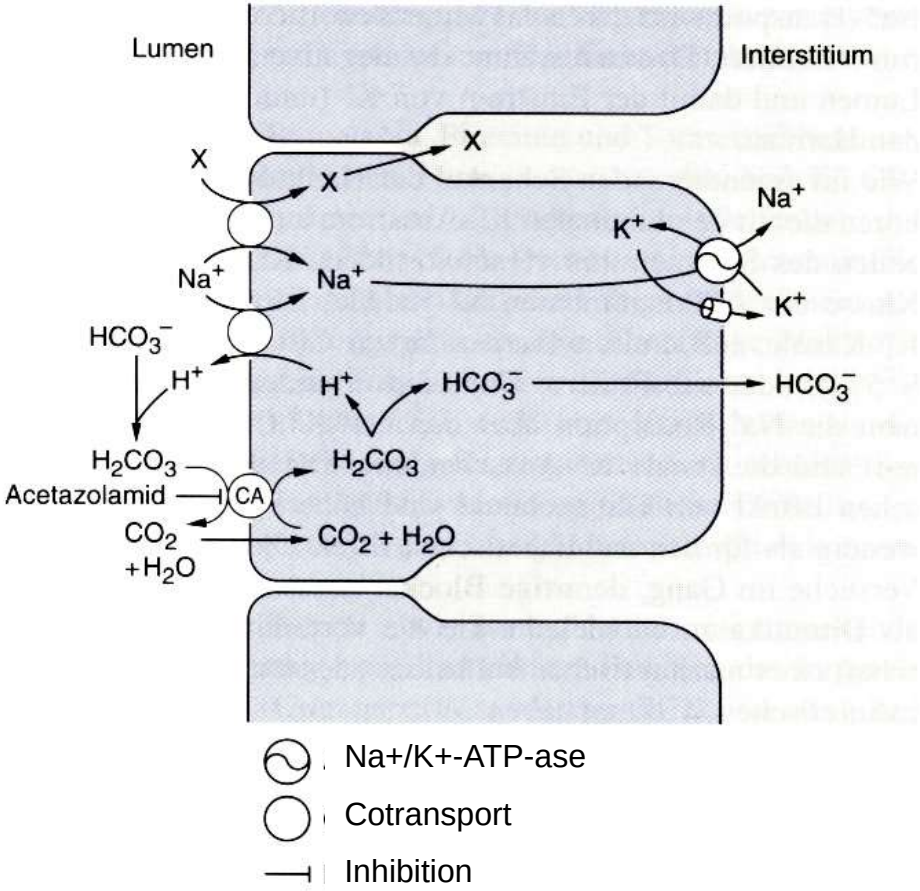

proximaler Tubulus
Glomerulus
distaler Tubulus
67 %
9 %
290 mosm/l
Rinde
Mark
3 %
20 %
granuläre Zellen
afferente Arteriole
Henle Schleife
Sammel-rohr
1200 mosm/l
1 %
Macula densa
Glom. Epithel (Podozyten)
efferente Arteriole

Groups of diuretics and their targets

- 1. Primarily salt excreting diuretics:
  - Carbonic anhydrase inhibitors – proximal tubules
  - Loop diuretics – ascending limb of Henle-loop
  - Thiazids – distal tubules
  - K+-sparing diuretics – upper part of the collecting tubules
- 2. Primarily water excreting diuretics
  - ADH-antagonists – lower part of the collecting tubules
- 3. Osmotic diuretics
  - Proximal tubules and the total lenghth of the nephron

Carbonic anhydrase inhibitors mechanism of action





Consequences of the inhibition of the carbonic anhydrase

- 1. Loss of HCO_3^-
- 2. Alkalic urine
- 3. Metabolic acidosis
- 4. Decreasing plasma bicarbonate concentration – decreasing bicarbonate filtration – decreasing Na^+ excretion – decreasing diuresis
- 5. Increasing proton secretion due to acidosis – acidic urine

Carbonic anhydrase inhibitors: drugs

- Acetazolamide
- Dorsolamide
- Dichlorphenamid
- Methazolamide

Indications of carbonic anhydrase inhibitors

- 1. Glaucoma
- 2. Meniere's syndrome
- 3. Acute mountain disease
- 4. Chronic metabolic alkalosis
- 5. Epilepsy

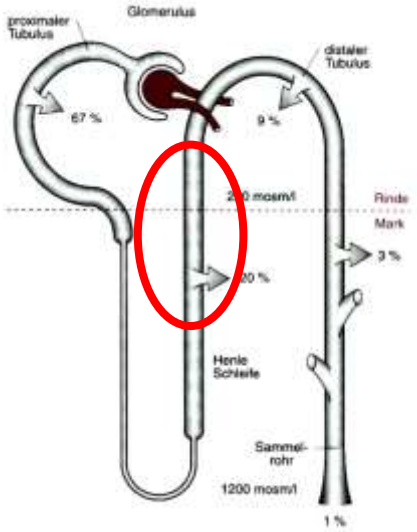
Side effects of carbonic anhydrase inhibitors

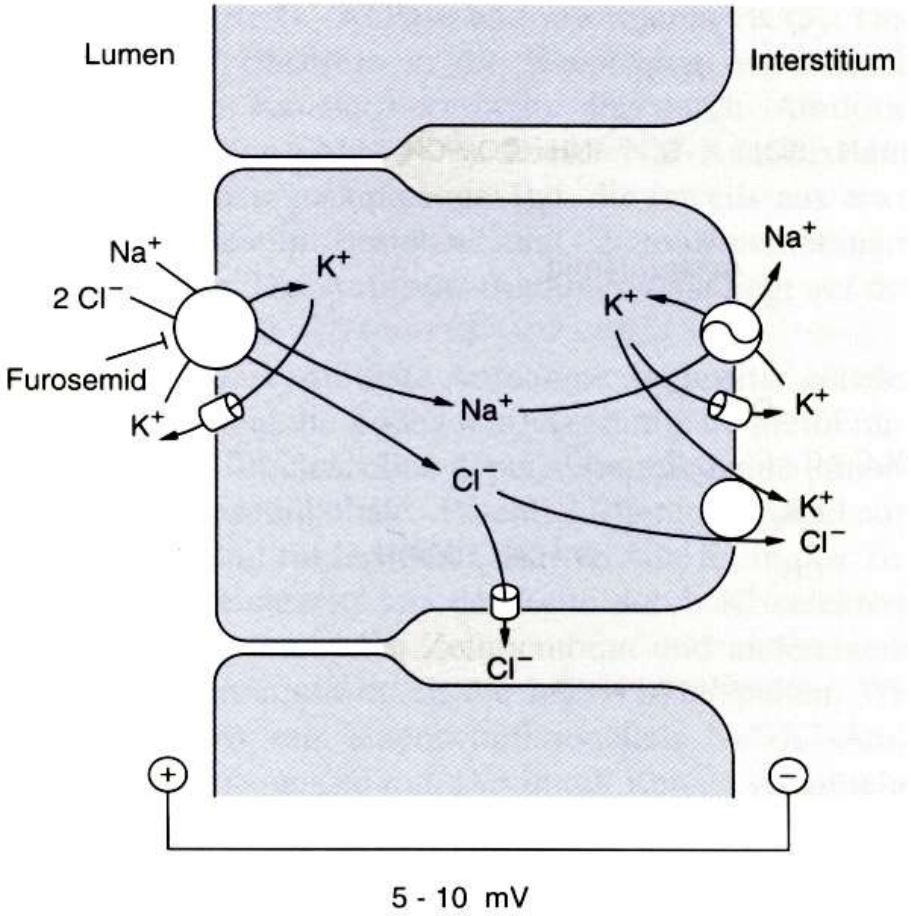
- Hyperchloremic metabolic acidosis
- Hypokalemia
- Paresthesia
- Somnolence
- Interstitial nephritis
- Renal stones (cystin and $Ca_3(PO_3)_2$)
- Bone marrow suppression

Loop diuretics: mechanism of action and representative drugs

- They inhibit the $Na^+/K^+/2Cl^-$ symporter in the ascending limb of Henle-loop
  - Furosemide (and other sulfonamide structures)
    - Torsemid
    - Bumetanide
    - Piretamide
  - Etacrynic acid (and its derivatives)
    - Indacrinone
    - Tycrinafen

Loop diuretics: mechanism of action





Consequences of the action of the loop diuretics

- 1. Na^+ és K^+ ions stay inside the loop
- 2. increasing water excretion
- 3. decreasing osmotic gradient
- 4. the originally positive lumen potential (luminar membrane is more hyperpolarized than the basolateral = transepithelial potential) becomes negative – increasing Ca^{++} and Mg^{++} excretion
- 5. increasing PG synthesis (PGs have diuretic and vasodilating effect
- 6. increasing RBF and renin secretion
- 7. K^+ loss

Indications of loop diuretics

- Acute pulmonary edema (left ventricule failure)
- Congestive heart failure
- Resistant edemas
- Acute renal failure
- Chronic renal failure
- Hypercalcemia
- Poisonings – alkalic metals, alkalic earthmetals (except Li)
- Poisonings – halogenids
- Gout (etacrynic acid and its derivatives)

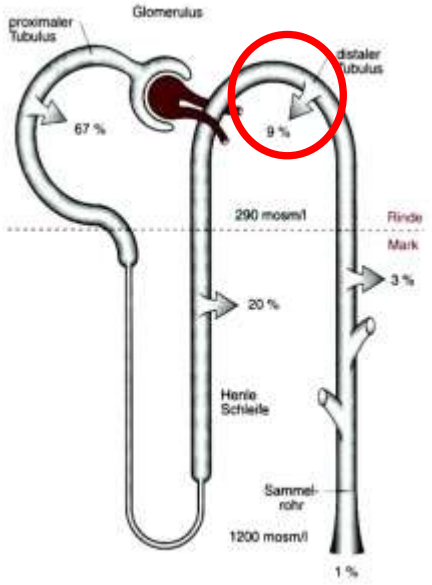
Side effects of loop diuretics

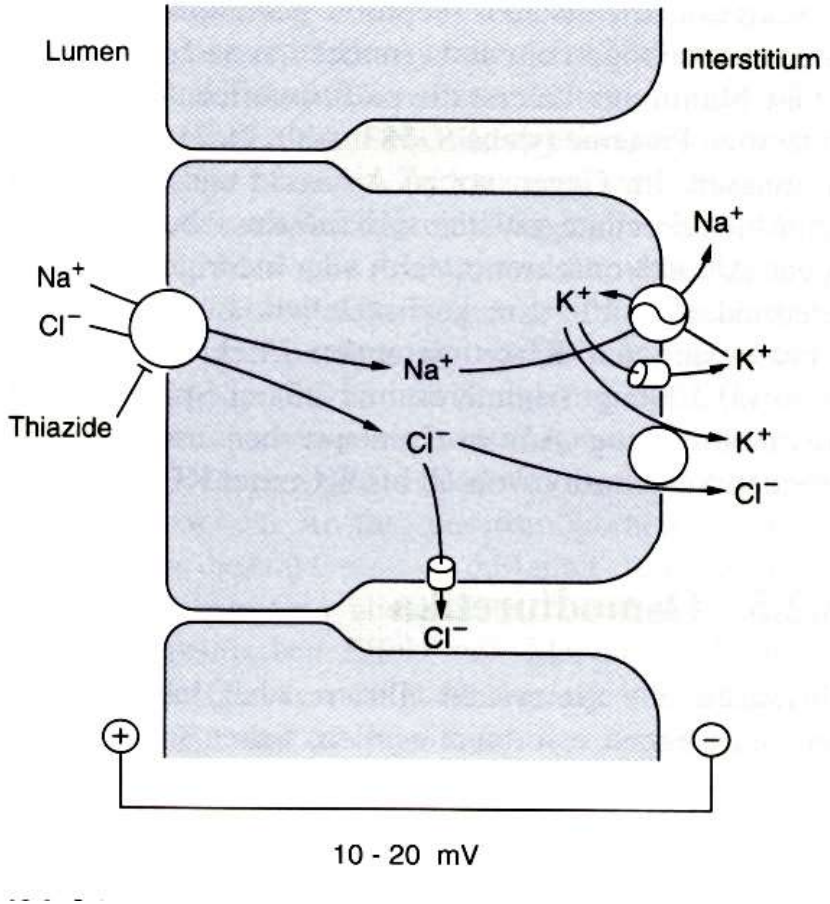
- Hypokalemia !!!
- Transient deafness
- Metabolic alkalosis
- Interstitial nephritis (sulfonamide structures)

Thiazides: mechanism and drugs

- They inhibit the NaCl reabsorption in the distal convoluted tubules
- They stimulate the PTH-dependant Ca reabsorption in the distal tubules (due to the decreased IC Na concentration the activity of the basolateral Na/Ca exchanger increases – increasing Ca reabsorption)
- Drugs:
  - Hydrochlorothiazide
  - Clopamide
  - Indapamide
  - Chlorthalidon

Mechanism of action of thiazides





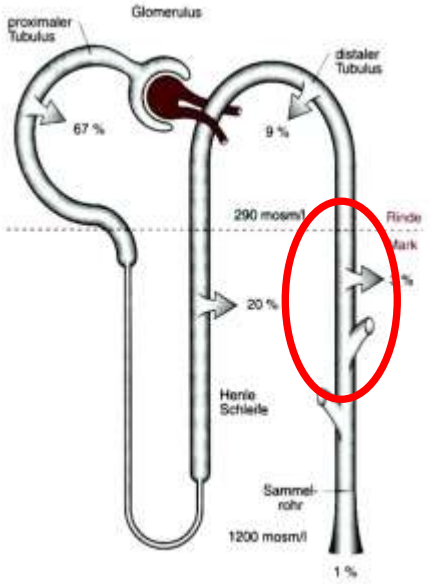
Indications of thiazides

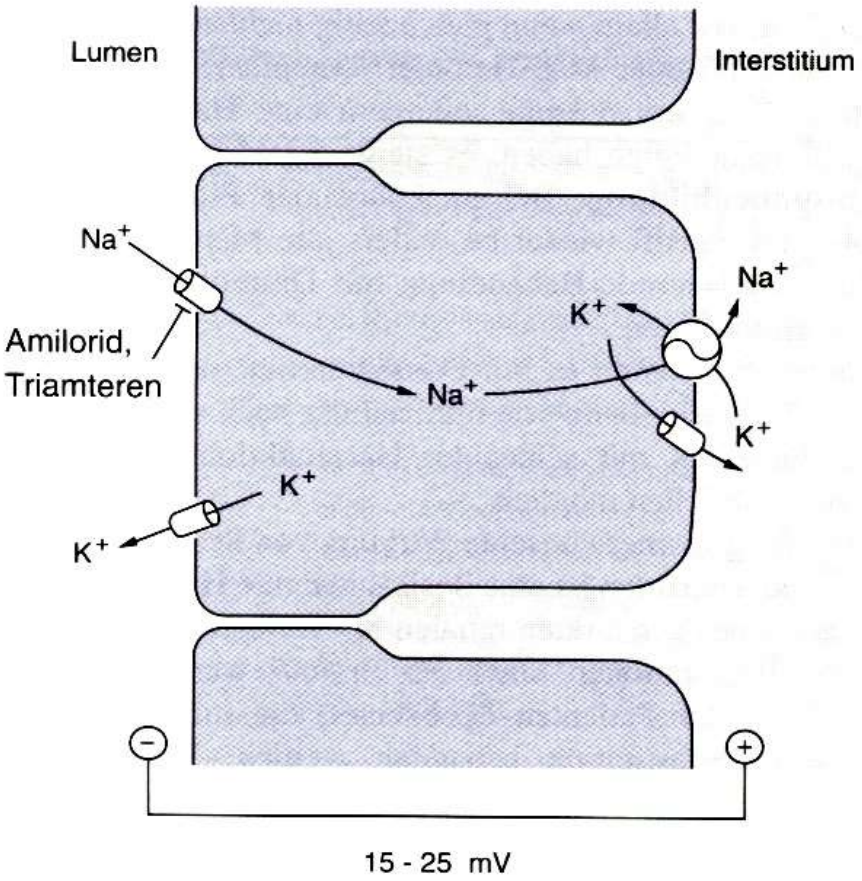
- 1. Congestive heart failure
- 2. Hypertension
- 3. Idiopathic nephrogenic hypercalciuria
- 4. Nephrogenic diabetes insipidus

Side effects of thiazides

- 1. Hypokalemia
- 2. Metabolic alkalosis
- 3. Decreased glucose tolerance
- 4. Weakness, fatigue
- 5. Impotence
- 6. rarely:
  - Hemolytic anemia
  - Pancreatitis
  - Acute pulmonary edema
  - Cholestatic jaundice

Potassium-sparing diuretics





K-sparing diuretics
aldosterone antagonists

- Spironolactone
- Canrenone
- Eplerenone
- They act in the cells of the collecting tubules on aldosterone receptors. !Not from the luminar side!
- They inhibit the expression of the aldosterone-dependent Na^+/K^+-ATP-ase and the luminar Na^+-transporters
- They act slowly, must be given several times a day but very effective

Indications and side effects of the aldosterone antagonists

- Indications:
  - Primary hyperaldosteronism (Conn's syndrome)
  - Secondary hyperaldosteronism
    - Congestive heart failure
    - Liver cirrhosis
    - Nephrosis
  - Hypertension (eplerenone)
- Side effects
  - Hyperkalemia
  - Metabolic acidosis
  - Gynecomastia (probably binds to sex hormone receptors)

K-sparing diuretics
inhibitors of the Na+-transporter

- Amilorid
- It inhibits the Na^+ reabsorption in the upper collecting tubules and, as a consequence, the K^+ excretion
- It is indicated for hypertension most commonly combined with thiazides

ADH-antagonists

- Tolvaptan, canivaptan (Li^+ ion, demeclocycline)
- In the lower part of the collecting tubules the inhibit the effect of ADH $\Rightarrow$ no aquaporin channel $\Rightarrow$ increasing water excretion
- Indications:
  - SIADH, congestive heart failure

Osmotic diuretics

- Mannitol, isosorbid, glycerin, urea
  - 1. In the proximal tubules they inhibit the Na^+ reabsorption.
  - 2. They reduce the intracellular volume, therefore increase the extracellular volume, decrease the viscosity of blood, inhibit the renin secretion. RBF increases so they withdraw NaCl from the medulla.
- They must be given parenterally, very strong diuretics
- Indications: acute renal failure, cerebral edema