Classification of Drugs

- Reduction of preload
  - Diuretics
  - Nitrates
- Reduction of afterload
  - hydralazine
- Reduction of preload and afterload
  - ACE inhibitors and angiotensin receptor blockers
  - β-adrenoceptor blocker
- Stimulation of myocardium
  - Digoxin

Classification

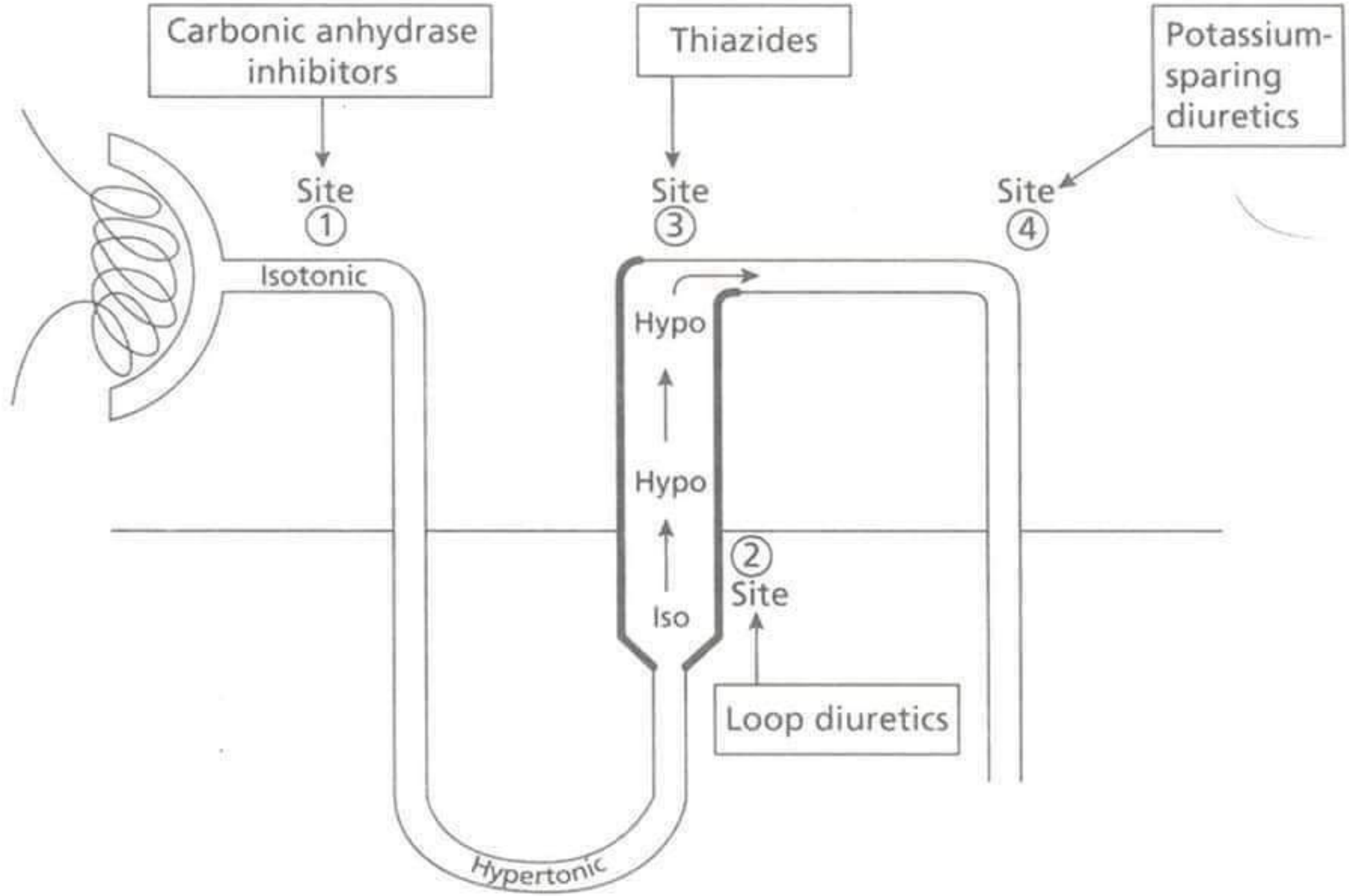
- Diuretics
- Cardiac glycosides
- Vasodilators
- β- blockers
- Sympathomimetic amines
- Phosphodiesterase inhibitors

Diuretics

- Loop diuretics : Frusemide, Bumetanide
- Thiazide : hydrochlorothiazide
- K+ sparing diuretics : Spiranolactone, amiloride, tramterene

Site and Mechanism of Action

- Loop diuretics
  - thick ascending limb
  - inhibit N^+-K^+- $2Cl^-$ co-transport
  - used in severe cardiac failure
- Thiazide diuretics
  - cortical diluting segment
  - inhibit Na^+ - K^+
  - used in mild to moderate cardiac failure
  - Not effective if GFT <30 ml/min


Carbonic anhydrase inhibitors
Site ①
Isotonic
Thiazides
Site ③
Potassium-sparing diuretics
Site ④
Hypo
Hypo
Iso
② Site
Loop diuretics
Hypertonic

Promote Na^+ and water excretion

↓

Reduce ECF volume

↓

Decrease preload

↓

Improve ventricular efficiency

Cardiac Glycosides

Aglycone (steriod nucleus with an attached lactone ring) with one or more sugar moieties attached to it.

Potent action on the heart , hence referred to as cardiac glycosides

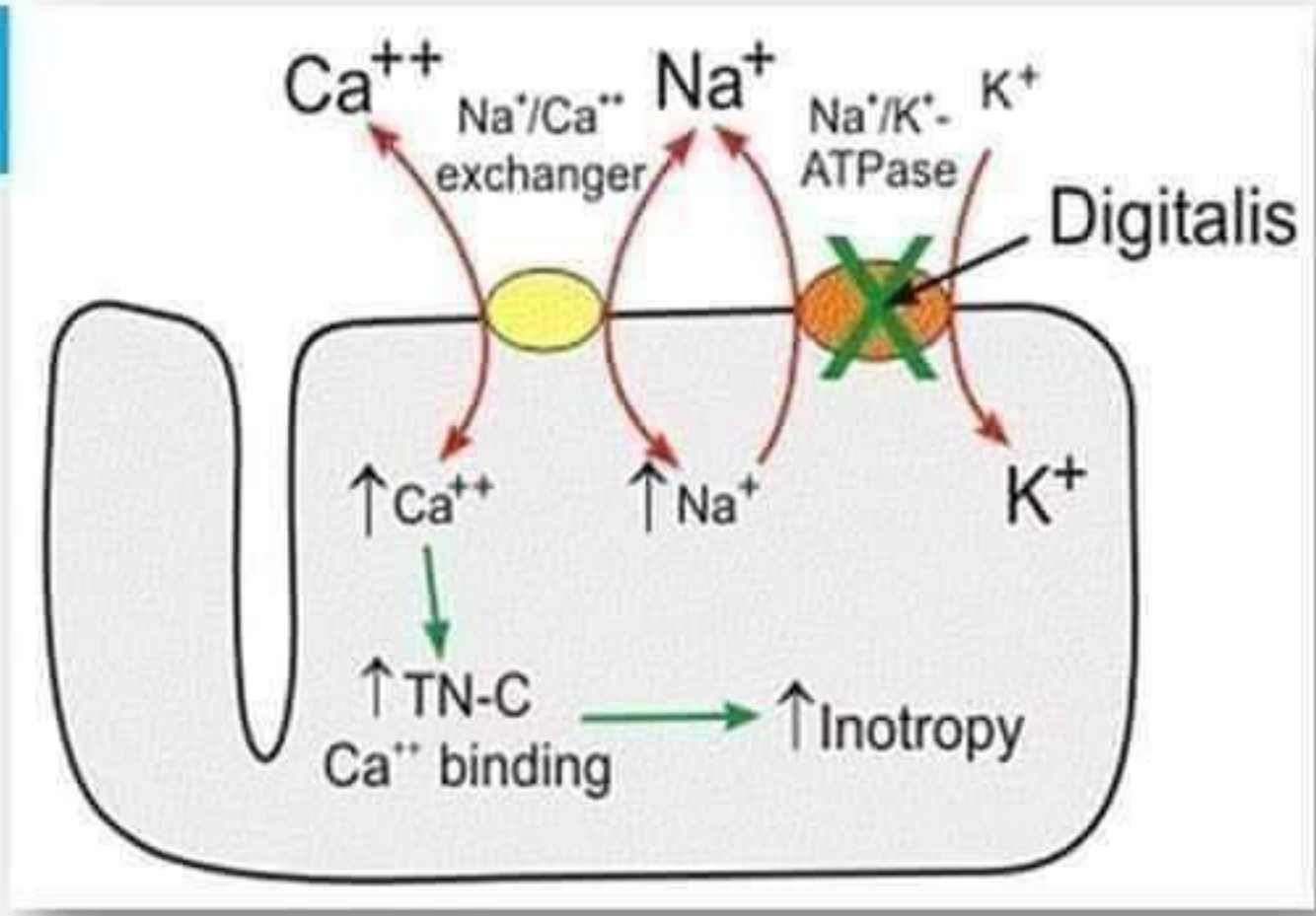
Sources

- *Digitalis pupurea* : Digitoxin
- *Digitalis lanata* : Digoxin, Digitoxin

The utility of digitalis in the treatment of heart failure was shown by William Withering.

Mechanism of Action

Direct



Indirect Enhance vagal activity

Reduced SA and AV node activity

Mechanism of Toxicity

- Cardiac glycosides bind to and inactivate the Na^+/K^+ ATPase pump on the cytoplasmic membrane of cardiac cells
- As a result intracellular Na^+ concentration increases
- This affects the Na^+/ Ca^+ exchange channels resulting in an increase in intracellular Ca^+ that leads to increased force of contraction

Uses

- Atrial fibrillation
- Atrial flutter
- Heart failure
  - benefit chiefly by direct action

Pharmacokinetics

- Digoxin is eliminated 85% unchanged in the kidney
- Remainder is metabolized in the liver
- $T_{1/2}$ is 36 hours
- Usually administered orally
- Hypokalaemia and hypomagnesaemia potentiate adverse effects of digoxin

Side effects

- Ventricular arrhythmias
- Heart block
- Anorexia and vomiting
- Disturbance in colour vision
- Gynaecomastia
- Mental effects

Treatment of Digoxin Toxicity

- Atropine for bradycardia
- Iv phenytoin for ventricular arrhythmia
- Fab fragment of the antibody to digoxin (Digibind)
- Temporary pacing
- DC shock for ventricular fibrillation

Drug interaction

- Verapamil, nifedipine, Quinidine and amiodarone increase plasma concentration of digoxin
- Increased likelihood of AV blocking with verapamil and β-blockers.

Vasodilators

- Predominant venodilatory → reduce preload

  eg; Nitrates

  some effect on arterioles

- Predominant arteriolar dilating effect

  → reduce afterload

  eg; hydralazine, minoxidil, nicorandil

  causes reflex tachycardia and fluid retention

- Mixed arteriolar and venodilators

  → reduce both pre and afterload

  eg; ACE inhibitors, ARBs, sodium nitroprusside

  Tachycardia is rare

ACE inhibitors

- First line drugs in the treatment of Chronic heart failure
- Action
  - inhibit conversion of angiotensin I to II
  - retard or reverse cardiac remodelling or hypertrophy
- Side effects;
  Cough, angioedema and neutropenia

Angiotensin-receptor blockers (ARBs)

- Eg; Losartan, Candesartan
- Competitively block AT-receptors on the heart, peripheral vasculature and kidneys
- As effective as ACE inhibitors
- Mainly used for those who cannot tolerate ACE inhibitors

IV sodium nitroprusside and nitroglycerin are used for severe heart failure.

β-blockers

- Metoprolol, bisoprolol and carvedilol
- Useful in mild to moderate heart failure
- Acts through β-adrenergic blocking effect on the heart
- Therapy should be carefully supervised

Sympathomimetic amines : Dopamine

- Catecholamine with conc. dependent haemodynamic effects

  Low conc. Selectively dilates renal, mesenteric and coronary blood vessels by acting on D_1 receptors → increases GFR and UOP

  Moderate doses stimulates β1- receptors → increase myocardial contractility and cardiac output

  tachycardia is less prominent

Useful in heart failure with renal impairment

At high concentration (>10 µg/kg/min)

→ generalized vasoconstriction

- increases afterload and

reduces blood flow to renal and other

vital organs

Sympathomimetic Amines: Dobutamine

- Synthetic catecholamine
- Act on $\beta_1\beta_2$ and α_1 receptors
- has selective inotropic effect and increases cardiac output
- In therapeutic doses, it has little effect on BP and heart rate.
- TPR is generally not affected (counterbalancing of α and β effects)