

- Relaxation

Salbutamol : β_2 : dilator, also inhibits release of mediators from Mast cells.

methyl xanthines (e.g. caffeine and theophylline) : therapeutic doses: (probably) by antagonising adenosine at adenosine receptors.
Higher dose: PDE inhibition, intracellular Ca^{2+} release

Ipratropium bromide : anti-histamine : aerosol inhalation. Quaternary compound \rightarrow lipid solubility is low, not absorbed into circulation.

- Uterine SM :

- Contraction:

NA (α_1)

ACh

Oxytocin : cause regular contraction of uterus for parturition
(β site)

Ergometrine : Sustained contraction : reduce the risk of post-partum haemorrhage.

Prostaglandin E₂ and E₂₂ : rhythmical contractions of pregnant of non-uterus

- Relaxation:

Salbutamol : in premature labour : relax uterine SM.

Local anaesthetics & antiarrhythmic drugs [Note W-2]

- Vasoconstrictor for prolonging the action of local anaesthetics (LAs)

NA, AD, felypressin : Prolong action, reduce circulatory toxicity.
↳ Vasopressin receptor | specific.

- Amide and ester LAs

Amide: lidocaine, prilocaine : slowly catabolised in the liver.

Ester: procaine, tetracaine, benzocaine.

- Methods of administration of local anaesthesia.

Surface ana: Applied to mucous membrane as solution, spray, jelly or lozenge (e.g., cornea, mouth and pharynx).

Lidocaine is good. Benzocaine poorly soluble, used as powder.

Lidocaine + prilocaine form a non-crystalline mixture

("eutectic mixture of LA" or EMLA: applied directly to the skin and produces completely anaesthesia in about 1 hr.

Infiltration ana: anaesthetize nerve ending. (details on note)

Large amount needed: danger of systemic toxicity & intravascular injection etc. Lidocaine, prilocaine & procaine are good. Vasoconstrictors used most often, but avoided in extremities → can cause ischaemic tissue damage

Nerve block ana: Subarachnoid space **Procaine**, **tetracaine** and **cinchocaine** are used. Many dangers: respiratory paralysis.

Epidural ana: to epidural space, diffuse to block nerve roots (Not spread to brain), used in obstetrics

Intravenous regional ana: distal to a cuff ~~is released~~. LA retrogradely diffuses into the tissue. Danger of toxicity if cuff prematurely released.

— anti-dysrhythmic drugs:

Class 1a — **quinidine**, **procainamide**, **disopyramide**: Prolongs repolarisations.
(effect less than Class 3)
Treat supraventricular and ventricular dysrhythmias.

Class 1b — **Lidocaine**, **mexitilie**, **tocainide**, **phenytoin**.

Associate & dissociate from Na^+ channels rapidly (within single beat).
Small slowing of AP rise but channels are blocked following peak: any premature beat is inhibited.
Preferentially block inactivated Na^+ channels.

IC — slow association and dissociation: level of block constant through cardiac cycle.

Less selectivity towards inactivated channels, not selective for damaged myocardium.

Treat atrial fibrillation, re-entrant dysrhythmias.

Class I^I : β -blockers : Propranolol, alprenolol, metoprolol.

blocking β_1 , block excitatory effects of sympathetic activity
Reduce slow inward Ca^{2+} current, SA pacemaker activity
and slowing AV conduction.

Treat tachyarrhythmias (e.g. atrial fibrillation) provoked by sympathetic activity.

III : K^+ channel blockers — amiodarone, sotalol (also class II)

Prolong cardiac AP and increases refractory period

amiodarone used to treat supraventricular and ventricular

dysrhythmias (but long half-life and numerous side effects)

IV : Ca^{2+} channel blockers : verapamil, diltiazem

inhibits L-type Ca^{2+} slow inward current, indirectly
reducing T_I current.

slow AV conduction, inhibit ectopic beats.

Treat supraventricular tachycardia.

— Individual drugs :

Quinidine : optical isomer of quinine

Side effects : hypotension ... [Note]

Procainamide : An analogue of procaine, similar anaesthetic actions.

Substitution of amide for ester bond, resistant to
hydrolysis by plasma cholinesterase. Suitable for systemic use.

Lidocaine : intravenous (i.v.) to prevent or abolish dysrhythmias (e.g. during
cardiac surgery), very short plasma half-life : rapid
metabolism by liver, continuous infusion required.

Toxic effect on CNS : excitement, disorientation, risk of
convulsion.

Propantheline (and other β -receptor antagonist)

Inhibition of slow response (Ca^{2+}) and slowing of A-V conduction. Used in atrial dysrhythmias and also to prevent exercise-induced ventricular extrasystole.

— Other therapeutic possibilities:

— Cardiac glycosides: Cause dysrhythmias by $\uparrow [Ca^{2+}]$.
Also cause partial A-V block.
Reducing ventricular rate in atrial fibrillation or flutter.

— Adenosine:

Potent blocker of AV nodal conduction.
(can terminate AV nodal re-entrant
supraventricular tachycardias)

— Electrical defibrillation. Used in conjunction with drug treatment.

— Implanted electrical pacemaker: only reliable way to treat heart block.

Diuretics. [Note 12-1]

Diuretics reducing water reabsorption

Cytosolic carbonic anhydrase **acetazolamide** (weak diuretic). Reduces H^+ supply to the tubular fluid and reduce HCO_3^- bicarbonate reabsorption.

Loop (of Henle reabsorption) diuretic — **furosemide**: block the NKCC ($Na^+/K^+/Cl^-/Cl^-$) co-transporter (K^+ can flow back to tubular fluid so there is a net excess of anion transport transcellularly). The net excess of anion drives further Na^+/K^+ /divalent cations (Ca^{2+} & Mg^{2+}) across the paracellular shunt → disrupting this process (NKCC transport) also decreases Ca^{2+} and Mg^{2+} reabsorption. Side effect: ↑ plasma glucose and uric acid. Much greater natriuresis than thiazides. Loop diuretics may block VSM NKCC: vasodilation.

Thiazides block the Na^+/Cl^- co-transporter in the distal convoluted tubule. Used to treat hypertension and heart failure (higher dose). Effect partly a direct consequence of the diuretic action. Partly by reducing vascular smooth muscle tone: fall in peripheral resistance. Relative importance hard to establish. Side effect: hypokalemia, increased plasma glucose, uric acid and lipids. (Adverse effects relatively uncommon) K^+ channel opening for VSM relaxation: vasodilation.

Both K^+ sparing { **Spironolactone** inhibits the mineralocorticoid receptor by competing with aldosterone. They act on a nuclear receptor within the tubular cell. The receptor enables a greater expression of ENaC channels and Na^+/K^+ pumps.

Amiloride blocks the ENaC Na^+ channels.

Other substances:

ototoxic substances: furosemide (Loop diuretics), aminoglycoside antibiotics, vancomycin.

Non-steroidal anti-inflammatory drugs (NSAIDs) attenuate and even may abolish the natriuretic and direct vascular effects of diuretics.
(Possible because NSAIDs inhibit prostaglandin synthesis)

Other diuretics can be found on the table in the Note:

Xanthines (e.g. caffeine, aminophylline): Adenosine receptor blocker.

Osmotic manitol: ↑ filtrate osmolarity → reduce gradient between tubular fluid and blood.

Renin-angiotensin system:

Angiotensin II can increase the release of ADH (vasopressin) from the Posterior pituitary → retention of water.

Promotes vasoconstriction, cardiac hypertrophy ~~and~~, kidney damage.

Aldosterone: binds to mineralocorticoid receptor → water retention.

Angiotensin-converting enzyme inhibitors: (ACE)

Captopril (now often replaced by enalapril, ramipril, lisinopril)

cause small fall in blood pressure (BP) in normal individuals, much greater reduction in hypertensive patient. In treating heart failure, co-administered with diuretics. ACE inhibitor reduces aldosterone production: ↓ K⁺ excretion (↓ ENaC); (Both pre- and post-load are reduced)
So not administered with potassium sparing diuretics.

Angiotensin II antagonist losartan : acts on angiotensin receptors : (No bradykinin-accumulating effect, unlike ACE inhibitor, so no dry cough as the side effect)

Antidiuretic hormone (ADH) = vasopressin.

Details of ADH in Note.

ADH release is inhibited by alcohol and increased by nicotine, angiotensin II.

Desmopressin : analogue of ADH : less vasoconstriction.

Chlorpropamide enhances the renal response to ADH.

Proximal convoluted tubular cells secrete and absorb weak acids:
"weak acid transport system" favours the actions of many drugs. (see Note)

Probenecid (probucid) can prolong the plasma half-life of drugs (e.g. penicillin) by blocking the transport system.

It can also promote the excretion of urate by blocking its reabsorption in the treatment of gout

Changing pH of the urine

(useful in cases such as urinary tract infection where drugs are more active in acidic or alkaline solution.)

Carbonic anhydrase inhibitor : alkalinize urine.

Citrate [a mixture of Na^+ and K^+ salts given by mouth] is metabolized via the Krebs cycle with generation of bicarbonate : alkalinize urine.

Amino chloride : acidify urine.

Heart failure [Note 12-2]

Diuretics:

- ① Loop diuretics furosemide
- ② Aldosterone antagonist spironolactone
- ③ Thiazide diuretics: bendroflumethiazide (bendrofluazide)
- ④ Potassium sparing: amiloride, triamterene

① First line therapy ② also K⁺-sparing as ④.

Adverse effects: ①②③④ can cause hyponatraemia. ①③ hypokalaemia.
(some) ②④ hyperkalaemia.

Angiotensin Converting Enzyme inhibitors (ACE-I)

Ramipril, enalapril: Inhibits Renin - Angiotensin - Aldosterone pathway. Prevents angiotensin I → II by ACE. Reduce vasoconstriction and water retention (aldosterone).

Adverse effects: first dose hypotension, dry cough (bradykinin accumulation), renal impairment, hyperkalaemia.

Angiotensin II receptor antagonist

Losartan: Block angiotensin receptor

Adverse effects: hypotension, worsening renal failure.

B-adrenoceptor antagonist

Carvediolol, bisoprolol: Antagonise activation of the sympathetic nervous system (some activation routes are harmful) as well as the renin angiotensin system (sympathetic output may ↑ renin release from juxtaglomerular cells). Adverse effects: tiredness, hypotension, impotence ...

Cardiac glycosides (Inotropes)

Digoxin increases the force of cardiac contraction = improves symptoms of heart failure

Adverse effects: (usually associated with excessive dosage): anorexia (厌食症), vomiting, cardiac arrhythmias.

Vasodilators — Ca^{2+} antagonists

Nifedipine, hydralazine

↳ inhibits L-type VGCC

Reduce pre- and after-load.

Adverse effects: hypotension, headache, flushing, tachycardia ...

β_1 agonist (Inotrope)

Dobutamine: rapid response - \uparrow intracellular levels of cAMP.

Phosphodiesterase (type III) inhibitors (Inotropes)

Milrinone, enoximone: Increase intracellular levels of cAMP,

\uparrow myocardial contractility.

Adverse effect: proarrythmic.

Details about the inotropes: Cardiac glycosides.

Structures on Note, a 5-membered lactone ring for activity.

Long-/medium-/short-acting glycosides: Digoxin / Digitalin / Ouabain
(differ in the sugar residues.)

Glycosides ① ↑ force of myocardial contraction.
(direct effect) ② ↑ excitability and automaticity of contractile and pacemaker cells.

(Vagal effects) ① Sinus bradycardia: excessive slowing of the heart in toxic dose.

② ↑ refractory period of A-V node and slow A-V node conduction.
(Beneficial in cardiac failure associated with atrial fibrillation or flutter.)

(Extra-cardiac actions on Note)

Cardiac glycosides frequently used with other adjuncts:

↓ BP { Vasodilators e.g. nifedipine (relax blood vessels more than heart)
diuretics ...
(other in Note)

Treatment of overdose: digitalis antibodies

bind free glycosides
Lidocaine (= lignocaine) / phenytoin

Anti-dysrhythmic

Phosphodiesterase (PDE) inhibitors in congestive heart failure (CHF)

Non-selective drugs: Caffeine, theophylline, aminophylline (important for asthma treatment)

Milrinone, enoximone: ↑ cAMP by inhibiting PDE-3

(Used in CHF refractory to glycoside or diuretic treatment)

PDE-3 found in VSM and heart: ↑ heart contractility (prolong Ca^{2+} influx)

VSM: vasodilation.

PDE-4 in lungs: inhibited by rolipram (important in asthma)

PDE-5 in the corpus cavernosum SM: inhibited by sildenafil (Viagra)

β_1 -Antagonist [bs% reduction in mortality]

Carvedilol ($\alpha_1 + \beta_1$) Bisoprolol (β_1): Reduce sympathetic stimulation of the heart. Considered first line therapy with ACE-inhibitors (e.g. enalapril) + spironolactone (block aldosterone receptor)

* To note: ACE-inhibitors initially decrease aldosterone, however this is transient.