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Antiarrhythmic Drugs. Week 4 Pharm

CLASS 1A Na Channel block (intermediate dissociation i.e moderate blockade)

* ganglion blocking properties.

Used for: AF, Aflutter, SVT, VT

Eg procainamide (anticholinergic) - depresses SA + AV node but also vagal block. Prolongs AP/QRS/ERP/QT

Toxicity: QT prolongation, TdP, Lupus syndrome, N&D, HYPOTENSION

PK: IV/IM/PO, hepatic metabolism to NAPA + renal elimination.

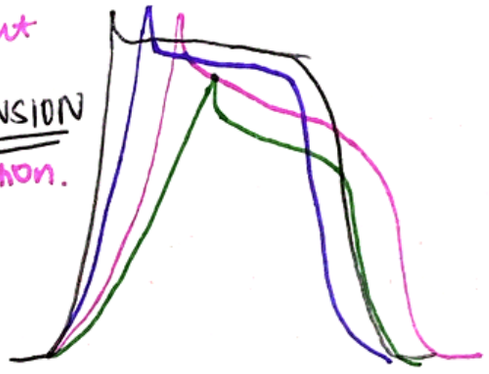
$t_{1/2}$ 3-4 hours

Eg Quinidine - As above actions but ~~better~~ poorly tolerated.

Good GIT absorption - hepatic metabolism

Significant risk of torsades due to ↑↑ QTc prolongation.

Amiodarone also class 1A actions: Blood dyscrasia.



Myocyte action potential.

CLASS 1B Na channel block w rapid dissociation i.e weak block

↓ERP

Used for: VT

Eg: Lidocaine (*lignocaine*) - arrhythmias assoc. w MI (post cardioversion)

PK: IV only due to ↑1st pass metab. $t_{1/2}$: 1-2hrs

binds to acute phase reactant · Liver metabolism.

Blocks active + inactive Na Ch's = not resting greater effect in cells w longer AP i.e perkinje + ventricular > atrial

Low toxicity → potential for ↓BP from myocardial dep.

Eg. Mexiletine - orally active lidocaine analog

$t_{1/2}$ = 8-20hours. clearance reduced by drugs that ↓ liver blood flow i.e cimetidine/propranolol

Na Channel blockade

1C > 1A > 1B

↑Effective refractory period

1A > 1C > 1B (decreases!)

can precipitate torsades DP!

interrupts tachycardia from reentry

from action on K^+ channels (non specific)

NB: Lignocaine does not affect AV conduction

CLASS 1C: Na channel block w slow dissociation i.e Strong block

For life threatening SVT/VT.

Eg. Flecainide - blocks Na + K channels strongly (no ↑AP & NO QTc↑) ↑ERP

PK: well absorbed, $t_{1/2}$ 20hours, hepatic + renal elimination

For normal hearts only → exacerbates arrhythmias in pts w prior VT/MI/PVCs.

Propafenone - similar to above $t_{1/2}$ 5-7 hours w some Beta blocker activity

moricizine - withdrawn

CLASS 2 - Beta Blockers (sympatholytic)

→ or can be partial agonists → prevent enhanced SNS activity.

Used for: HTN, Angina/MI, arrhythmias, heart failure, AORTIC DISSECTION

General MOA: bind to β adrenoreceptors + block Norad/adrenaline from binding

↑β1 in heart w some β2 → Gs protein → cAMP → L-type Ca^{2+} ch's → ↑Ca into cell

↑ chronotropy (HR) & inotropy (contractility)

Blockade causes: ↓HR, ↓contractility, ↓conduction velocity, ↓ relaxion rate. ↑effect w ↑SNS activity

Vascular SM has β2. Gprotein → cAMP → inhibits myosin light chains → SM relaxation

so blockade can cause some ↑ vasoconstriction.

Antiarrhythmic effect: from inhibition of sympathetic influences

Sympathetic NS → ↑ SA node pacemaker current.

β blockers also ↑AP duration & refractory period.

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CLASS 3 Prolongation of action potential (K^+ channel block)

For: AFlutter, Reentry, VT/VF.

Bind to and block K^+ channels in phase 3 of AP = delays repolarisation.
QT prolongation! But no torsades.

Eg: **Amiodarone**: $t_{1/2}$ 30–60 days (Rapid 3–16 days), class I, II, III, IV actions. ↓Risk of QTc → TdP.
Serious side effects → thyroid issues, pulm fibrosis.
used if ICD discharging a lot OR cannot manage VT/VF/PVCs x many.
can cause bradycardia + AV node block so c/I in pts w previous known blocks.
Hepatic metab
CYP450
lots of interactions

ALSO: sotalol (also class II) prolongs QT + ERP.
dofetilide, ibutilide } No effect on AV conduction.

CLASS 4: Calcium Channel Blockers.

Rate control AF/flutter esp AVNRT.

Bind to L-type CaCh's in myocytes, pacemaker cells; vascular SM.
↓firing rate of aberrant pacemaker cells, ↓ conduction velocity + prolong repol. (esp. AV node)
Block AVNRT.
Anti arrhythmics are the NON-DIHYDROPYRIDINES.

VERAPAMIL: myocardial selective. $t_{1/2}$ 4-7 hrs. PO → BioAv. 20%. liver metabolism
PO onset 30mins
→ blocks activated + inactivated channels so ↑ effect in frequently firing cells i.e SA/AV node
→ suppress early + delayed after depolarisations. NEGATIVE INOTROPE
→ causes peripheral vasodilation.
→ If given in VT can cause ↓BP & VF.
→ can cause AV block (treat w atropine + β agonists)
cardiotoxic effects are dose related + avoidable
S/E: constipation, lassitude, nervousness, peripheral oedema

DILTIAZEM – cardiac + SM actions
PO onset >30mins, $t_{1/2}$ 3.7hours
– ↓arterial pressure without reflex tachycardia.

ADENOSINE Naturally occurring nucleoside, Binds A_1 G protein receptor → cAMP
Nucleoside $t_{1/2}$ 10sec.
Activates K^+ channels + Inhibits Ca^{2+} current (from cAMP)
⇒ hyperpolarisation of cells + suppression of Ca dependent AP in nodal cells
↑ effect on AV node
Tox: flushing, dyspnoea, hypotension, Afib, sense of doom, headache, chest pain.
90–95% effective in terminating SVT

Mg^{2+} 1g $MgSO_4$ over 20mins
MOA? understood → effect on Na/K/ATPase.
Even if (N) Mg levels
Membrane stabiliser → VT/SVT

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β-BLOCKERS

MOA: Antagonise the effects of catecholamines @ β adrenoceptors.

Carvedilol & Labetalol also cause α-1 blockade.

PK: Well absorbed PO.
Peak [] 1-3hours.
Varied bioavailability i.e propranolol – 1st pass metabolism @ lower doses.

Large Vd.

Propranolol + penbutolol cross BBB

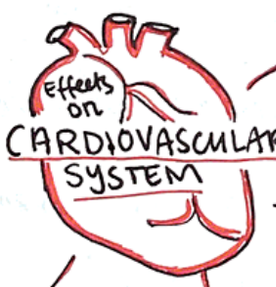
Esmolol $t_{1/2}$ 10mins.

Metoprolol + propranolol metabolised in liver.
CYP2D6 enzyme Δ informs clearance.
(poor metabolisers = 3-10fold ↑ [])

Used for
- ↓O_2 demand post MI.
- HTN (via ↓ CO)
- Arrhythmias (rate control)
- glaucoma
- heart failure (low+slow)
- hyperthyroidism (propranolol)
- migraines
- cirrhosis + varices (↓ portal venous pressure)
- infantile haemangiomas

β receptors Cellular mechanism
- Bind to receptor
- Gprotein activation
- Adenylyl cyclase
- ↑cAMP
- ↑Ca^{2+} in cell
- activate protein kinase

(blocked by β blockers)



Blocks B_2 vasodilation in peripheral vasc.

↓O_2 use by β

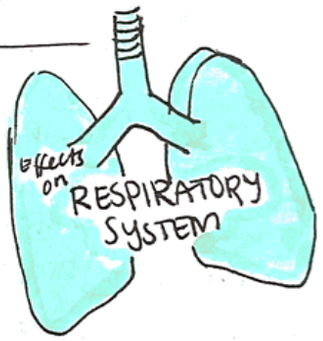
Negative inotropy

Negative Chronotropy → class II (don't use if AV block)

Slow AV conduction
↑PR interval

lower BP via ↓ renin release
(no hypotension in N people)

$β_2$ blockade in smc = ↑airway resistance (esp in asthmatics)



Timolol

↓IOP from ↓ aqueous humor production

Propranolol
- Non selective
- ~~Partial agonist~~
- Local anaesthetic action
- High lipid solubility (CNS)
- Elim $t_{1/2}$ 3-6hrs
- Dose dependent bioavailability (~30%)
- No effect on α → seizures

"also blocks Na+ channels" widening of QRS → VF arrest in overdose

Metoprolol
- $β_1$ selective
- $t_{1/2}$ 3-4hrs
- BioAv 50%.
- Vd >300L

OD = seizure

Esmolol
$β_1$, Rapid

Bisoprolol
- $β_2$ selective
- $t_{1/2}$ 9-12hrs
- BioAv 80%.

Labetalol
- α1 + ($β_1$/$β_2$)
- pregnancy HTN

Sotalol Class II & III
- overdose = asystole
- prolongs QT
- 100% bioavail.
- $t_{1/2}$ 12hrs.

β inhibits SNS activation of lipolysis

Δ's to VLDL + HDL ratio

can impair recovery from hypoglycaemia

Nebivolol
Most $β_1$ selective
vasodilation via NO effects

SIDE EFFECTS
- Bradycardia
- Cold hands + feet
- Vivid dreams
- Depression
- Worsening asthma
- cardiac decompensation
- hypoglycaemia
- fatigue
- hypotension
- interaction w/ Ca^{2+} Channel blockers can cause heart block
- hyperkalaemia (from ↓ insulin release)

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↑ GIT: nausea/vomiting/anorexia/diarrhoea.
CNS: chemo trigger zone, hallucinations.

verapamil + Amiodarone ↑digoxin [ ]

DIGOXIN

70% oral bioavailability
67% urinary excretion (2/3rds)
25% plasma bound
clearance 9L/h/kg
Vd 500
$t_{1/2}$ 39hrs

↑K inhibits binding (↓K facilitates)
↑Ca ↑action

MOA: Inhibits Na/K/ATPase
1. → ↑intracellular sodium
2. → ↑intracellular Ca^{2+} (+ve inotropy)
   → ↑extracellular K^+ (hyperkalaemia)
3. → dont treat w Calcium gluconate → will ↑ arrhythmias due to already high intracellular Ca.

Also enhances vagal tone = ↓SA/AV node velocity

Electrical effects:
Therapeutic dose
- SA node: ↓Rate
- Atrial muscle: ↓Refractory period.
- AV node: ↓conduction velocity ↑refractory period
- Perkinje system: slight ↓ refractory period
- ECG: ↑PRint, ↓QT, ⊤TWI

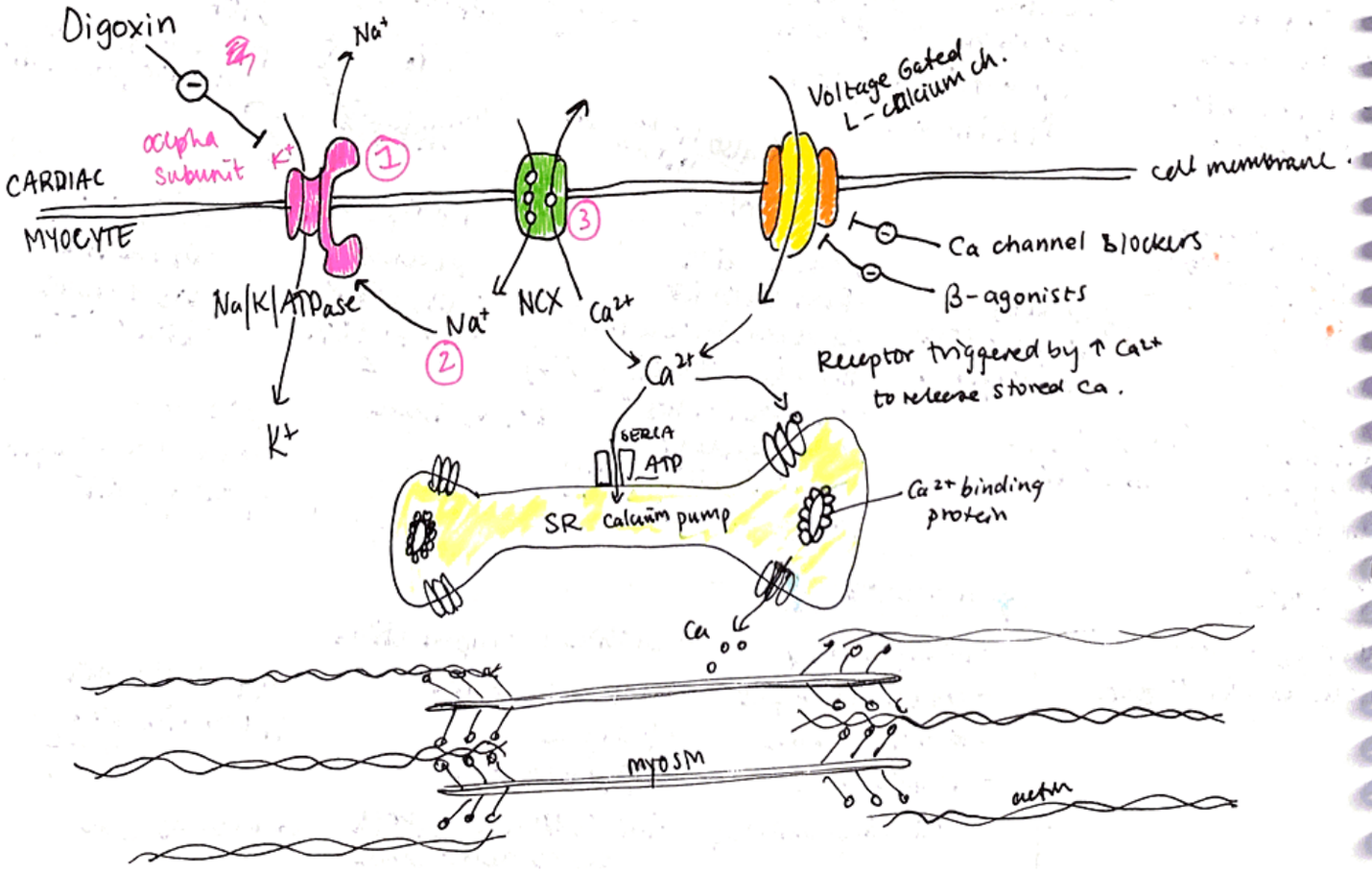
toxic dose
↓↓rate.
↓ref → arrhythmias
↓ "
extrasystole, Vtach, VF
Tachy, VT, VF, arrest.

NB ~~ACh~~ binds to M_2 @ heart
"reflex brady"

DOWNSTREAM EFFECTS

↑contractility = ↑CO
∴ ↓ stimulus for ↑ sympathetic output.
∴ ↓HR + ↓vascular tone
↑CO = ↑systolic fxn
↑End diastolic relaxation + ↓stress
∴ ↑heart size + O_2 req.

↑Renal blood flow = ↑GFR
⇒ ↓aldosterone driven Na^+ reabsorption.



Week 6 Pharmacology – CV III.

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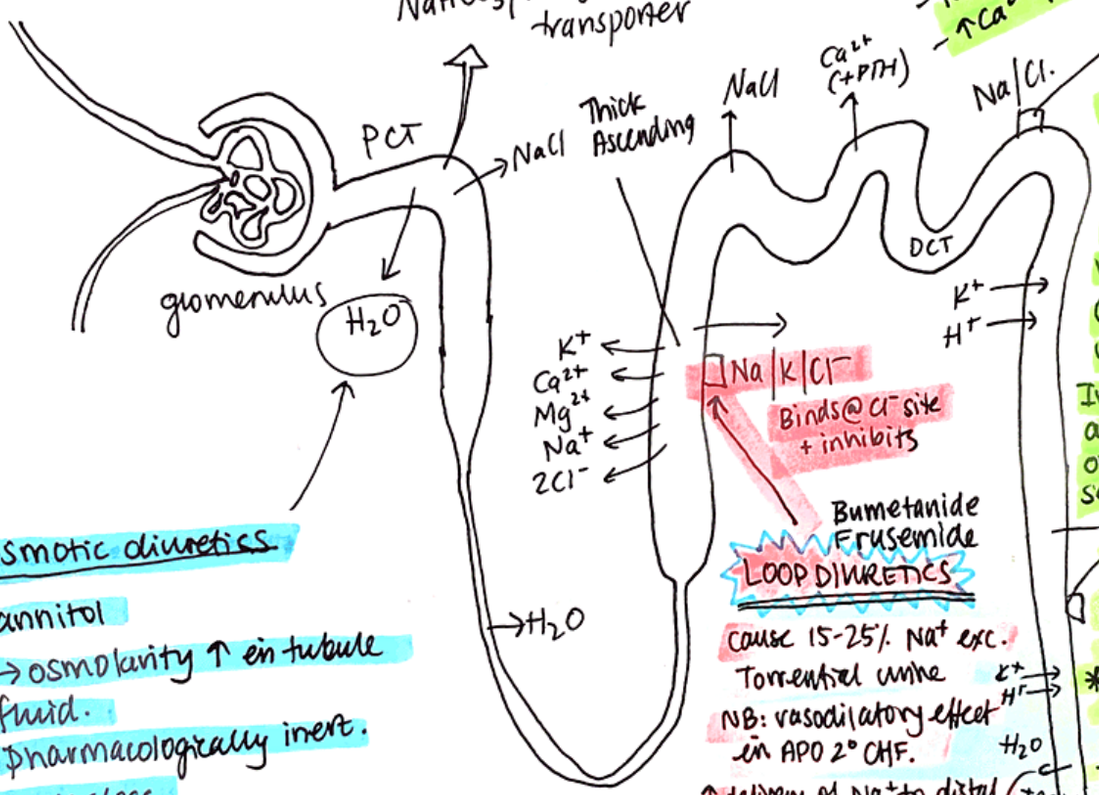
DIURETICS

↑ Na^+ & H_2O loss/excretion by the kidney
↓ Resorption of Na^+ (& Cl^-) ⇒ natriuresis
Direct or indirect (via filtrate content modification)



Used for:
- diabetes insipidus → nephrogenic (paradoxical effect)
- HTN
- Mild heart failure
- ↑ Ca^{2+} to prevent stones.

THIAZIDES
Hydrochlorothiazide
Bendroflumethiazide
Less powerful but better tolerated
Same electrolyte effects @ smaller magnitude.
Bind to Cl^- site / inhibits
↓ Ca^{2+} loss (benefit in OP)
vasodilator action.
Good PO effects
can be used w/ loops.

Impaired glucose tolerance from activation of K_{ATP} channels on islet cells.

Spironolactone (K+ sparing)
Anti-HTN effects + anti-androgen
active metab: canrenone (16 hrs)
Hyperkalaemia
GI upset
$t_{1/2}$ 10 mins
takes days for action to develop.
used when K+ loss is bad i.e also on digoxin
(structurally similar to progesterone)

Osmotic diuretics
Mannitol
↳ osmolarity ↑ in tubule fluid.
Pharmacologically inert.
↑ water loss
Problems → transient ↑ in ECF volume
↳ Risk of LV failure.

ACETAZOLAMIDE (Carbonic Anhydrase Inhibitors)
→ ciliary body, choroid plexus, prox renal tubules. (blocks bicarb reabsorption)
↑ excretion of bicarb w/ $Na^+/K^+/H_2O$
= ↑ flow of alkaline urine & metabolic acidosis
Self limiting due to depleting bicarb.
well absorbed PO.
used for glaucoma; ↓ CA reduced aqueous humor
mountain sickness
causes acidity in pH of CSF

Toxic effects:
- Hyperchloraemic metabolic acidosis
- Renal stones (PO_4, Ca^{2+})
- Renal K^+ wasting,
- Drowsiness, paraesthesia
- Hepatic encephalopathy in pts w/ cirrhosis 2° ↓ NH_4^+ clearance

PK:
✓ well absorbed PO ≈ 50%.
1hr PO vs 30 mins IV
secreted into PCT
Protein bound → In nephrotic syndrome they bind to tubule albumin + don't work.
$t_{1/2}$ 90 mins
Action 3-6 hrs

Problems → hypotension
→ hypovolaemia (pre renal AKI)
→ ↓ K^+ / Met Alkalosis / ↓ Mg
→ ↑ effects of digoxin
→ hyperuricaemia (gout)
→ dose related hearing loss

Longer $t_{1/2}$ w/ renal failure.

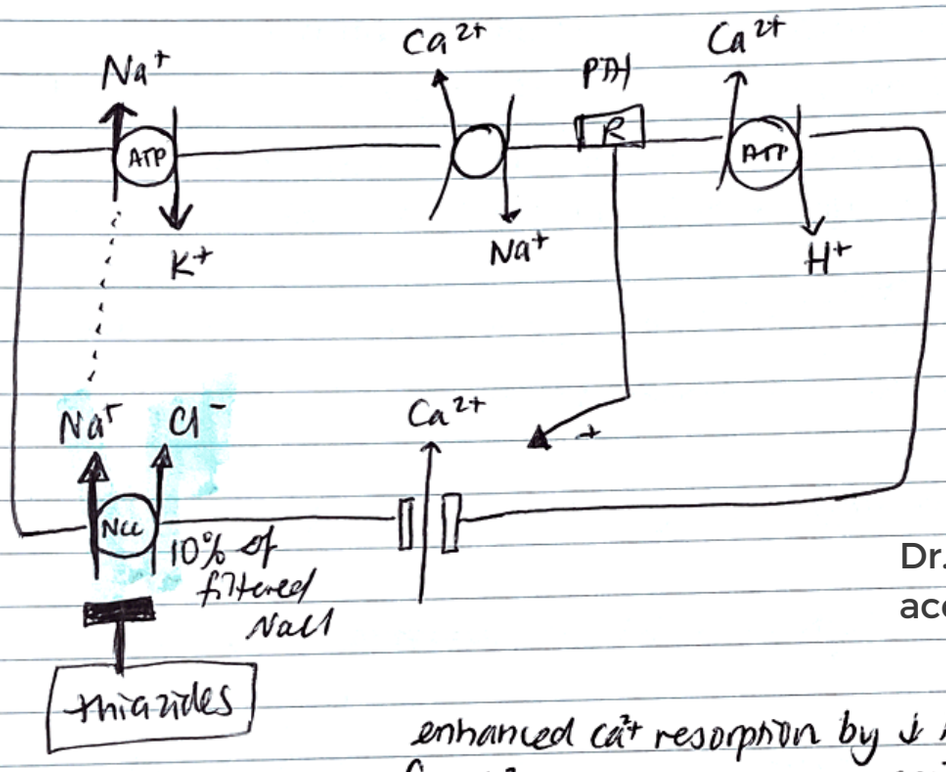
Used in: APO
- CHF
- Ascites
- Nephrotic Sy.
- Renal failure

DRUG INTERACTIONS: NSAIDs / Aminoglycosides / Anticoagulants / digoxin / Lithium

K+ sparing
Triamterene
= collecting duct
Amiloride

Thiazides

Distal convoluted tubule



OFF TARGET EFFECT

hyperpolarize pancreatic β-cells + ↓ insulin release → ↑ BGL.

Also hyperlipidaemia

enhanced Ca^{2+} resorption by ↓ intracellular $[Na^+]$ & causing more Na^+/Ca^{2+} exchange.
can unmask hypercalcaemia from other sources that was previously compensated.

can be used to prevent kidney stones 2° hypercalciuria.

Hyponatraemia.

→ hypovolaemia induced ↑ADH
→ ↓ dilution of urine
→ ↑ thirst.

Hypokalaemic metabolic alkalosis (also for loops)

→ Inhibition of Na resorption (hyponatraemia)
→ ↑ delivery of Na to collecting duct
→ ↑ Na ⇒ ↑ secretion of H^+ & K^+ in collecting duct.

Causes gout

ACE INHIBITORS

VIVA Q: MOA of ramipril, adverse effects, drug interactions

Inhibit: converting enzyme peptidyl dipeptidase (ATI → ATII) (ATII is a vasoconstrictor ∴ main effect is ↓ in vascular tone.)
also inhibits plasma kininase (same enzyme, diff name)
that inactivates bradykinin – a potent vasodilator
so ↑ bradykinin in circulation = ↓BP.
ATII → aldosterone secretion ∴ ↓ATII = ↓aldosterone = ↓Na/H_2O retention = ↓BP.
2/4
∘∘ effects from inhibition of RAAS + stimulating kinins.

Works to ↓ BP by ↓ PVR
CO x HR ∅ significantly affected (no reflex tachy)

Used in:
1. CHF post MI: preserves LVEF
2. Diabetic nephropathy (↓proteinuria)
3. Hypertension.

PK: drugs – prodrugs converted by hydrolysis in the liver.
captopril
elanopril – ~~prodrug~~ 10-20mg daily
benazepril.
perindopril
ramipril.

Adverse effects & drug interactions
- dizziness
- headache
- weakness
- loss of taste

Hypotension.
Angioedema & cough/wheezing

- contraindicated in pregnancy – foetal renal failure.
- hypotension in hypovolaemic patients.
- can alter sense of taste
- interacts w K^+ supps or K^+ sparing diuretics → ↑K (via blocking of aldosterone)
- NSAIDs can block the bradykinin mediated vasodilation & reduce antiHTN effects.
- Significant 1st dose antihypertensive effect.
- Known to cause renal failure in adults soon after starting.
- Eliminated by the kidney.
- Causes lithium toxicity

VIVA Q: What advantages do ARBs have over ACE inhibitors? (Irbesartan, telmisartan)
- No effect on bradykinin so reduced cough, angioedema
- More complete inhibition of ATII actions (some other ATII via other enzymes)