



Prof dr Aleksandar Raskovic

# DIRECT VASODILATORS

# Direct vasodilators

- Minoxidil (one of the most powerful peripheral arterial dilators)
- Opening of  $K_{ATP}$  channels, efflux of  $K$ , lose of  $Ca$  and smooth muscle relaxation
- Used for severe hypertension (in addition to diuretics and beta blockers)
- Per os
- Unwanted effects
- Due to arterial vasodilation – flushing and headache

# Direct vasodilators

- Reflex tachycardia (which can be diminished by the use of beta blockers)
- Oedema – most marked in the ankles
- Salt and water retention through stimulation of RAA system (can be reduced by concurrent use of diuretics)
- Hirsutism (to be extreme hairy) – rarely used in women

# Direct vasodilators

- Hydralazine
- Activate guanylate cyclase
- Increased conc. of cGMP intracellularly
- Smooth muscle relaxation (arterias)
- Per os, injection
- N acetylation
- Slow acetylators – systemic lupus erythematosus (SLE) – like syndrome

# Direct vasodilators

- Headache, dizziness
- Tachycardia, flushing, hypotension, fluid retention
- Sodium nitroprusside
- Increased conc. of cGMP intracellularly
- Smooth muscle relaxation (arterias and veins)
- Used for hypertensive crisis and the most severe types of heart failure
- Orthostatic hypotension, tachycardia, arrhythmias !!

# Direct vasodilators

- Diazoxide is a potassium channel activator
- relaxation in smooth muscle by increasing membrane permeability to potassium ions
- This switches off voltage-gated calcium ion channels
- which inhibits the generation of an action potential

# Direct vasodilators

- diazoxide is used as a vasodilator in the treatment of:
- Malignant (severe) hypertension associated with renal disease
- diazoxide also inhibits the secretion of insulin from the pancreas
- thus it is used to counter hypoglycemia in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.

# Centrally acting antihypertensive drugs

- Methyldopa
  - 1. Alpha 2-adrenergic agonist
  - Decreases noradrenaline release in peripheral tissue
  - 2. False precursor of dopamine, NA and adrenaline (alfa methyl dopamin, alfa methyl NA, alfa methyl adrenaline cannot stimulate receptors)
- Indication: gestational hypertension (also known as pregnancy-induced hypertension (PIH))
- According to FDA – category B
- When methyldopa was first introduced, it was the mainstay of antihypertensive treatment, but its use has declined on account of relatively severe adverse side effects

# Centrally acting antihypertensive drugs

- side effects:
- depression, suicid, nightmares
- sedation, agitation or restlessness
- memory impairment
- Xerostomia (dry mouth)
- Parkinsonian symptoms such as muscle tremors, rigidity, hypokinesia, and/or balance or postural instability

# Centrally acting antihypertensive drugs

- Bradycardia, hypotension (though this may also be considered a therapeutic benefit)
- Orthostatic hypotension (also known as postural hypotension)
- Hepatitis, hepatotoxicity, or liver dysfunction or damage
- Haemolytic anaemia
- Hyperprolactinemia, gynecomastia in males, and/or amenorrhoea or absence of menstrual cycles in females
- Sexual dysfunction including impaired libido, desire, and drive

# Centrally acting antihypertensive drugs

- Clonidine
- stimulates presynaptic  $\alpha_2$  receptors in the brain:
- Decrease NA release, decreased cardiac output and peripheral vascular resistance (vasoconstriction), lowering blood pressure. The net effect is a decrease in sympathetic tone.
- It is an agonist on the  $I_1$ -receptor (imidazoline receptor) – reduced NA release
- Higher doses – stimulation of  $\alpha_1$  adrenoreceptors - vasoconstriction

# Centrally acting antihypertensive drugs

- Indication:
  - Hypertension, migraine, menopausal flushing
  - neuropathic pain, opioid detoxification
  - FDA approved to treat ADHD - attention deficit hyperactivity disorder
- Caution: sudden discontinuation can cause rebound hypertension due to a rebound in sympathetic outflow

# Centrally acting antihypertensive drugs

- Side effects:
- Dry mouth (50 % of patients)
- Sedation, depression
- Bradycardia
- Raynaud's phenomenon
- Fluid retention

# Centrally acting antihypertensive drugs

- Moxonidine
- An agonist of imidazoline I<sub>1</sub> receptors
- Decreases sympathetic outflow
- The result is fall in blood pressure with no reflex tachycardia
- Adverse effects: dry mouth, fatigue, dizziness
- Indication: hypertension

# Reserpine - central and peripheral sympatholytic agent

- Reserpine irreversibly blocks the vesicular monoamine transporter. This normally transports free norepinephrine, serotonin, and dopamine from the cytoplasm into storage vesicles
- unprotected neurotransmitters are metabolized by MAO and therefore never reach the synapse
- Final result: decreased sympathetic drive, lowered heart rate, decreased blood pressure and vascular resistance
- Indication: hypertension; long  $t_{1/2}$

# Reserpine

- Well tolerated in lower doses (0,1 mg) when is used in combination with diuretics and vasodilators
- As monotherapy (in higher doses - 1 mg) can cause depression
- Other side effects: dry mouth, nasal stuffiness
- Sedation
- peptic ulcer
- Salt retention

# $\alpha_1$ adrenergic antagonists

- Prazosin, terazosin, doxazosin
- Selective antagonists of the  $\alpha_1$  adrenergic receptors
- They antagonize the effect of NA
- Lower blood pressure
- Decrease peripheral resistance (prevent vasoconstriction)
- Severe orthostatic hypotension can occur, particularly after first dose (“first dose effect”)

## $\alpha_1$ adrenergic antagonists

- It is recommended that the initial doses be small and administered at bedtime for a first few days
- Other indication - Benign prostatic hyperplasia (alpha 1 receptor stimulates contraction of sphincter of urinary bladder)
- Tamsulosin and alfuzosin are selective alpha 1A receptor antagonists
- Alfa 1 A receptor is located in sphincter and prostata, and these drugs possess little antyhypertensive action