2. INHIBITORS OF CATHECOLAMINE SYNTHESIS

Inhibitors of tyrosine hydroxylase: METYROSINE
Mechanism of action: inhibit tyrosine hydroxylase → inhibitor of dopamine synthesis.
Indications: treatment of pheochromocytomas (inoperable or metastatic); it is associated with Phenoxybenzamine.

3. CENTRALLY ACTING SYMPATHOLYTIC AGENTS

Classification:
3.1. Acting mainly on CNS:
   - Selective agonists on I1 imidazoline receptors: Moxonidine, Rilmenidine
   - Agonists on α2 presinaptic adrenergic receptors and I1 imidazoline receptors: Clonidine, Apraclonidine, Brimonidine, Tizanidine, Dexmedetomidine
   - Other mechanism of action: Methyldopa, Guanabenz, Guanfacine

3.2. Acting on CNS and peripherally: Reserpine
3.3. Acting mainly peripherally: Guanetidine, Guanadrel, Bethanidine, Debrisoquin.

Selective agonists on I1 imidazoline receptors
Moxonidine, Rilmenidine
Mechanism of action
- agonist on I1 imidazoline receptors;
- block sodium influx in renal juxtaglomerular cells.

Pharmacodynamic effects
- central effects: reduce sympathetic tone and noradrenaline release (does not cause sedation);
- peripheral effects:
  • reduce the release of peripheral norepinephrine → reduce blood pressure
  • block sodium influx in renal juxtaglomerular cells → natriuretic effect.

Indications
- Rilmenidine: hypertension (mild/moderate)
  • hypertension in young patients;
  • hypertension in patients with left ventricular hypertrophy;
  • hypertension in patients with diabetes mellitus;
  • hypertension in patients with cerebral atherosclerosis;
  • hypertension in patients with renal failure (creatinine clearance > 15 ml/min);
  • hypertension in patients with hepatic failure.
- Moxonidine: moderate hypertension.

Adverse reactions (rare): dry mouth; nausea, constipation; at high doses: decrease libido, headache, depression.

Contraindications
- severe depression;
- severe renal failure (creatinine clearance < 15 ml/minute);
- Raynaud’s syndrome.
- avoid the association with alcohol, neuroleptics, barbiturates, tricyclic antidepressants.

Benefits:
- They do not cause metabolic effects.
- They are not hepatotoxic / nephrotoxic.
- They do not cause marked hypotension. Cardiac dynamics is not affected.
- They do not cause sedation. They do not influence intellectual activity.
- They do not cause depression.
- They do not influence sexual activity.

Stimulants selective II imidazoline receptors cause immediate effects, which gradually increases (the maximum intensity is after 3-4 weeks of treatment). They are administered in one dose per day, as monotherapy or in combination with diuretics, calcium channel blockers or inhibitors of angiotensin converting enzyme.

**Agonists on α2 presinaptic adrenergic receptors and II imidazoline receptors**

| CLONIDINE, APRACLONIDINE, BRIMONIDINE, TIZANIDINE, DEXMEDETOMIDINE |
|---|---|

**Mechanisms of action**
- agonist on imidazoline II receptors;
- agonist on α2-presynaptic receptors;
- partial agonists of α1 and α2-postsynaptic receptors.

**Pharmacodynamic effects**
- because it is agonist on α2 – presynaptic receptors determine:
  - inhibition of sympathetic tone (decrease in systolic and diastolic blood pressure) and increase in parasympathetic tone;
  - orthostatic hypotension induced by clonidine is rare and low,
    - iv administration of clonidine determines first a short period of increase (by stimulating α1 postsynaptic receptors), which is followed by a decrease in systolic and diastolic blood pressure
    - at therapeutic doses (orally), clonidine does not determine the pressor effects,
    - in overdose, clonidine can induce severe hypertension;
  - sudden interruption of the administration of clonidine (or missing 1-2 two doses) → withdrawal syndrome: increase blood pressure, tachycardia, headache, nervousness, sweating;
  - decrease in renal vascular resistance;
  - in the eye: reduction of aqueous secretion of ciliary processes
    - this effect is stronger for clonidine derivatives (Apraclonidine, Brimonidine, Dexmedetomidine), so they are indicated for closed angle glaucoma;
  - in renal juxtaglomerular cells: inhibition of the synthesis and release of renin;
  - in exocrine glands: reduction of salivary glands secretion (dry mouth) and gastrointestinal glands (constipation);
- other effects on the CNS:
  - sedative - hypnotic, indifference to the environment (Dexmedetomidine determines the most powerful hypnotic effect);
  - inhibition pre- and postsynaptic spinal receptors determine a muscle relaxant effect important for the treatment of localized spasm of skeletal muscle and treatment of spasm produced by the pyramidal lesions (Tizanidine, Dexmedetomidine);
  - block the release of norepinephrine → depressions;
  - determine the inhibition of symptoms produced by abrupt cessation of opiates:
    - inhibition of nausea and vomiting;
    - by stimulation of α1 and α2 postsynaptic adrenergic receptors → anorectic effect;
- other pharmacodynamic effects:
Lecture 6: ADRENERGIC SYSTEM AND DRUGS. Adrenoceptor antagonist drugs and other sympatholytic drugs

Lecturer Cristina GHICIUC, MD, PhD

- by stimulation of \( \alpha_2 \)-presynaptic receptors (and due to the effect of partial antagonist on \( \alpha_2 \)-postsynaptic receptors) \( \rightarrow \) determine inhibition of nociception in the spinal dorsal horn and analgesic effect (Tizanidine, Dexmedetomidine);
- by stimulation of \( \alpha_2 \)-presynaptic receptors (and due to the effect of partial antagonist on \( \alpha_1 \) - postsynaptic receptors) \( \rightarrow \) determine inhibition of ejaculation;
- by \( \alpha_2 \) presynaptic receptor stimulation \( \rightarrow \) inhibition of release of insulin, inhibition of the glycogenolytic and lipolytic effects of catecholamines, increase in plasma levels of triglycerides and decrease in levels of high density lipids (HDL cholesterol) \( \rightarrow \) increase atherogenesis;
- partial stimulation of adrenergic receptors \( \alpha_1 \) \( \rightarrow \) stimulation of gluconeogenesis;
- partial stimulation of vascular cerebral \( \alpha_1 \) postsynaptic receptors \( \rightarrow \) moderate vasoconstriction.

**Indications:**

**- Clonidine:**
  - alternative in the treatment of hypertension;
  - alternative in the treatment of glaucoma;
  - migraine, other pulsatile headaches;
  - opioid dependence (reduce withdrawal syndrome);
  - as an alternative in the treatment of diarrhea (experimentally).

**- Apraclonidine:** glaucoma (preoperatively and after laser therapy).

**- Brimonidine:** glaucoma (which does not require surgery).

**- Tizanidine:**
  - muscle relaxant for the treatment of localized spasm of skeletal muscle and treatment of spasm produced by the pyramid lesions;
  - as an analgesic.

**- Dexmedetomidine:**
  - glaucoma;
  - as an analgesic;
  - as a sedative - hypnotic;
  - as a muscle relaxant.

**Adverse effects**
- hypotension (rarely, low intensity);
- bradycardia;
- dry mouth;
- constipation;
- loss of appetite;
- sedation, drowsiness (reduced for transdermal administration);
- depression, indifference to environment;
- metabolic disorders (increase in blood glucose, triglycerides);
- sexual disfunction;
- withdrawal syndrome with abrupt discontinuation of administration;
- local reactions at the transdermal delivery.

**Contraindications:**
- endogenous depression;
- pregnancy;
- severe renal failure;
- severe heart failure;
- bradyarrhythmias;
- AV block;

Lecturer Cristina GHICIUC, MD, PhD
- diabetes mellitus;
- severe dyslipidemia;
- peripheral vascular insufficiency, Raynaud's syndrome;
- pheochromocytomas;
- association with tricyclic antidepressants.

## Centrally acting sympatholytic agents with other mechanisms of action

**METHYLDOPA**

**Mechanisms of action:**
- is an analogue of L-dopa, which crosses the blood-brain barrier, then it is transformed into metabolites (alpha-methyl-noradrenaline and alpha-methyl-dopamine), which are stored in the vesicles of adrenergic neurons, where replace norepinephrine and are released by nerve endings with role of false mediator (cannot interact with postsynaptic adrenergic receptors);
- agonist on α2 presynaptic adrenergic receptor and on postsynaptic α1 receptors;
- agonist on dopamine receptors (including D2).

**Pharmacodynamic effects:**
- decrease in blood pressure (higher in the patients with hypertension);
- moderate increase in peripheral vascular resistance;
- decrease in heart rate and cardiac output (less than the effect induced by clonidine);
- reduction in plasma renin;
- block drainage of aqueous humor in the eye;
- pseudoparkinsonism, tardive dyskinesia.

**Pharmacokinetics**
- bioavailability → 25%, it has extensive first pass metabolism.
- it crosses the blood-brain barrier (an active mechanism); it does not cross the placenta.
- after oral administration, the maximum effect is reached after 4-6 hours and lasts longer than 24 hours (the action persists even after the disappearance from circulation).

**Indications:**
- treatment of essential hypertension
- it is drug of choice for the treatment of hypertension in pregnancy.

**Adverse effects**
- sedation, reduction of initiative, reduction of ability to concentrate, of attention, slowness in ideation (after long administration), sleep, drowsiness, nightmares, depression, dizziness;
- extrapyramidal symptoms;
- hyperprolactinemia (females and males);
- inhibition of salivary secretion, but also inhibition of nausea and vomiting;
- loss of appetite;
- constipation;
- edema;
- hepatotoxicity, autoimmune hepatitis;
- immunological reactions: fever, granulocytopenia, thrombocytopenia, hemolytic anemia, positive Coombs test.

**Contraindications:**
- depression,
- liver disease;
- Parkinson's disease;
- pheochromocytoma;
- glaucoma.

**Benefits:** the orthostatic hypotension is minimal; the hypotension during effort is rare.
GUANABENZ, GUANFACINE

**Mechanism of action:** adrenergic agonists $\alpha_2$ - presynaptic ($\alpha_2 >> \alpha_1$).

**Pharmacodynamic effects:**
- decrease blood pressure, decrease peripheral vascular resistance;
- decrease cardiac output;
- reduction of plasma renin.

**Pharmacokinetics:** cross the blood-brain barrier, cross the placenta, filtered during dialysis.

**Indications:** hypertension
- hypertension with increased plasma renin, in young adults;
- hypertension in patients with coronary artery lesions or ;
- hypertension in patients with a history of myocardial infarction;
- hypertension in patients with left ventricular hypertrophy.

**Contraindications:**
- pregnancy;
- depressions;
- pheochromocytoma;
- children under 12 years.

**Benefits:**
- reduction in plasma renin and in circulating catecholamines;
- are not nephrotoxic;
- sexual dynamics is not affected;
- No interference with digitalis, oral antidiabetics, oral anticoagulants, anti-inflammatory drugs.

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**Centrally acting sympatholytic agents with other mechanisms of action**

**RESERPINE**

**Source:** Rauwolfia sandwicensis (plant)

**Mechanism of action:**
- block the reuptake and storage of catecholamines in vesicles from terminal nerve ending of adrenergic neurons $\rightarrow$ depletion of norepinephrine, dopamine and serotonin;

**Pharmacodynamic effects:**
- in the CNS: sedation, mental depression, reduce the aggression, pseudoparkinsonism;
- periphery: decrease blood pressure, decrease peripheral vascular resistance, decrease cardiac output, bradycardia, depression of vascular sympathetic reflexes.

The optimal effects are achieved after 2-3 weeks of treatment.

**Pharmacokinetics:** drug rapidly crosses the blood-brain barrier.

**Indications:** hypertension (as an alternative, rarely used).

**Adverse effects**
- marked hypotension;
- asthenia, sedation, mental depression, pseudoparkinsonism, anxiety, nightmares;
- stimulate the release of gastrin $\rightarrow$ gastric hypersecretion,
- stimulate the appetite; weight gain;
- digestive spasms; diarrhea;
- congestion of the nasal mucosa;
- salt and water retention;
- sexual impotence;
- menstrual disorders;
- risk of breast cancer.
Contraindications: depression, peptic ulcer, acute gastroenteritis, acute colitis, epilepsy, Parkinson's disease, pseudoparkinsonism, pregnancy, young adults.

<table>
<thead>
<tr>
<th>Centrally acting sympatholytic agents with predominant peripheral action</th>
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<tbody>
<tr>
<td>GUANETIDINE, rarely used: GUANADREL, BETHANIDINE, DEBRISOQUIN</td>
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<tr>
<td><strong>Mechanism of action:</strong></td>
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<tr>
<td>- inhibition of noradrenaline release from sympathetic nerve endings;</td>
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<tr>
<td>- Guanethidine is captured in the nerve endings (the same mechanism as for norepinephrine), form covalent bonds with the storage granules, replacing norepinephrine ( \rightarrow ) a progressive depletion of norepinephrine from nerve endings.</td>
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<td><strong>Pharmacodynamic effects:</strong></td>
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<td>- reduction in systolic and diastolic blood pressure;</td>
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<td>- reduce the force of contraction of the heart; decrease in cardiac output;</td>
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<td>- severe bradycardia;</td>
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<td>- local anesthetic effect.</td>
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<td><strong>Pharmacokinetics:</strong></td>
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<tr>
<td>variable bioavailability(3-50%); renal elimination(50%); half-life=5days.</td>
</tr>
</tbody>
</table>

**Indications:** hypertension (as an alternative, rarely used).

**Adverse effects**
- orthostatic hypotension (increased during exercise, heat, alcohol intake), which can determine cerebral or myocardial ischemia;
- bradycardia;
- salt and water retention; edema;
- diarrhea;
- inhibition of ejaculation;
- weakness.

**Contraindications:** pheochromocytoma; association with tricyclic antidepressants, phenothiazine antipsychotics, cocaine, amphetamines.

Guanadrel: has properties similar to Guanethidine; the drug is indicated for the treatment of hypertension (as an alternative, rarely used).