ANTI ADRENERGIC DRUGS

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ANTI ADRENERGIC (SYMPATHOLYTIC) DRUGS

Drugs block the actions of circulating catecholamine (EP & NE) on adrenergic receptors

- Also inhibit the effects of adrenergic nerve stimulation

Classification of Sympatholytic drugs

A. Alpha (α) Adrenoceptor Antagonists

B. Beta (β) Adrenoceptor Antagonists

C. Alpha (α)+Beta (β) Adrenoceptor Antagonists

A. Alpha Adrenoceptor Antagonists

Block alpha (α) adrenoceptors

Classification of α antagonists

1) Non-specific $\alpha_1 + \alpha_2$ antagonists

Phentolamine & phenoxybenzamine

Cont.

2) Specific α_1 antagonists

Prazosin, doxazosin, terazosin, tamsulosin & alfuzosin

3) Specific α_2 antagonist

Yohimbine & tolazoline

Basic pharmacology of Alpha-receptor Antagonist Drugs

Mechanism of Action

Receptor Interaction

Reversible

↓

Dissociate

↓

e.g. Phentolamine & prazosin

Irreversible

↓

can not dissociate

↓

e.g.Phenoxybenzamine

Pharmacological Effects

A) Cardiovascular Effects

1) Antagonism of α-receptors of arterioles & veins → ↓ **PVR** → ↓ BP
2) Prevent pressor effect of usual doses of α-agonists → depressor effect; c/d ***epinephrine reversal***

cont

3) Postural hypotension → posture is changed from sitting to upright position →sudden ↓ BP (pooling of blood in extremities due to gravity)

4) Reflex tachycardia usually by non-selective blockers

cont.

B. Other Effects

1) **Nasal congestion** (dilatation of blood vessels of nasal mucosa)

2) Blocking of α_1 receptors of dilator pupillae muscles➔ Miosis+↓ intraocular pressure (phenox.)

3) Blocking of α_1 receptors of trigone+sphinctor muscles ➔ relaxation ➔ ↑ urinary outflow (phenox.)

Detailed properties of specific agents

1) Non-specific α_1 + α_2 antagonist

A) Phentolamine

- Imidazoline-derivative

Pharmacodynamics:

MOA

Blocks both α_1 + α_2-receptors

Cont.

Effects

- **Antagonism of α_1–receptors** (possibly α_2) of vascular sm.muscles → ↓ **PVR** → ↓ BP
- **Cardiac stimulation** in response to baroreflex mechanism
- **Antagonism of presynaptic α_2-receptors** →↑release of NE from sympathetic nerves →cardiac stimulation

cont.

- Inhibits response to **serotonin**; agonist of **muscarinic, H_1 & H_2 histamine receptors**

Pharmacokinetics:

- Limited absorption after oral intake, other properties are not well known
- Cont.

Clinical Use:

- Pheochromocytoma & male erectile dysfunction

Ad.effects:

- Tachycardia, arrhythmias, myocardial ischemia, diarrhea, ↑ gastric acid production

B) Phenoxybenzamine

Pharmcodynamics

MOA:

- Irreversible (covalent) binding to α-receptors (↑ selective for α_1) → long duration (14-48 h) blockade

cont

Effects:

- Inhibits reuptake of NE by pre-synaptic nerve terminals
- Blocks H_1, ACh & 5-HT receptors
- Blocks catechol-induced vasoconstriction ➔ ↓ BP during high sympathetic tone (upright position)
- ↑ CO ➔reflex effect + blockade of α_2 receptors

Pharmacokinetics of Phenoxybenzamine

- ✓ Usually given orally
- ✓ Absorbed after oral intake with low starting dose of 10-20 mg/d

Adverse effects

- ✓ Postural hypotension, tachycardia, nasal stiffness, inhibition of ejaculation, fatigue, sedation and nausea

2) Specific α_1 Antagonists

A) Prazosin

- Piperazinyl quinazoline, highly selective for α_1 receptors, low affinity for α_2 (↓ tachycardia)

MOA

- Blocks α_1 → ☞ relaxation of arterial and venous sm.muscles

Cont.

PK:

Extensively metabolized by liver, 50% drug is available after oral administration

B) Terazosin

MOA

Reversible α_1 selective antagonist

Uses

Hypertension & benign prostatic hyperplasia (BPH)

PK

Bioavailability ⇑

Half life is 9-12 h

C) Doxazosin

MOA

Highly selective for α_1 receptors, low affinity for α_2

Uses

Hypertension & BPH

PK: moderate bioavailability, longer half life of ~ 22 h, extensively metabolized

D) Tamsulosin

MOA: competitive α_1 antagonist, structurally d/f from others, greater selectivity for α_{1A}-sub type than α_{1B}

Uses: ↑ effective for BPH (α_{1A}); ↓effective for hypertension

PK: very high bioavailability, long half life (9-15h)

E) Alfuzosin

Quinazoline derivative

- Selective for α_1
- Little effect on human BP

3) Specific α_2 Antagonists

A) Tolazoline

Similar to phentolamine, rarely used clinically for pulmonary hypertension in new borne

B) Yohimbine

- Indole alkaloid; selective α_2 antagonist
- No clinical role; research drug

Ergot derivatives

Ergotamine, **dihydroergotamine**

Cause reversible α-receptor blockade, no clinical effect

Clinical pharmacology of α-receptor blocking drugs

1) Pheochromocytoma

- Tumor of adr.medulla; releases mix of EP, NE; patients have ↑BP, tachycardia,arrhythmia
- Major clinical use of phenox. & phentolamine

Cont.

- **Phenoxybenzamine** Used in

a) Preoperative episode =oral dose of 10-20 mg/d ➔☞increased in several days

b) Chronic treatment of inoperable or metastatic condition

c) **Phentolamine** used to manage ↑BP

2) Hypertensive emergencies

- Limited use of α-antagonist, only **Labetalol** is used

3) Chronic hypertension

Members of **prazosin** family are effective for mild to moderate systemic hypertension

Major adv.effect is **postural hypotension**; **dizziness**

4) Peripheral vascular disease

Phentolamine,prazosin,phenoxybenzamine ➔☞Raynaud'sphenomen; excessive reversible vasospasm in peripheral circulation

5) Local vasoconstrictor excess

Phentolamine reverse intense local vasoconstriction caused by infiltration of α-agonists into subcutaneous tissues

6) Urinary obstruction

a) Partial reversal of sm muscle contraction in enlarged prostate & in bladder base
b) Effect on cells in prostate & improve symptoms of BPH e.g. prazosin, doxazosin & terazosin useful for BPH + hypertensive patients

Cont.

c) Tamsulosin effective for those BPH patients having postural hypotension

7) Erectile dysfunction

e.g **Phentolamine**