

SYMPATHOLYTIC AGENTS (ADRENORECEPTOR BLOCKING AGENTS)

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ALPHA – ADRENERGIC BLOCKING AGENTS
BETA – ADRENERGIC BLOCKING AGENTS

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ALPHA-ADRENOCEPTOR BLOCKING AGENTS

- NON-SELECTIVE

- NON-COMPETITIVE

Eg. * Phenoxybenzamine

- COMPETITIVE

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Eg. * Phentolamine

* Tolazoline

* Ergotamine

SELECTIVE

ALPHA-1 Antagonists

Eg. * Prazosin

* Terazosin

* Doxazosin

* Alfuzosin

ALPHA- 1A Antagonist

Eg. * Tamsulosin

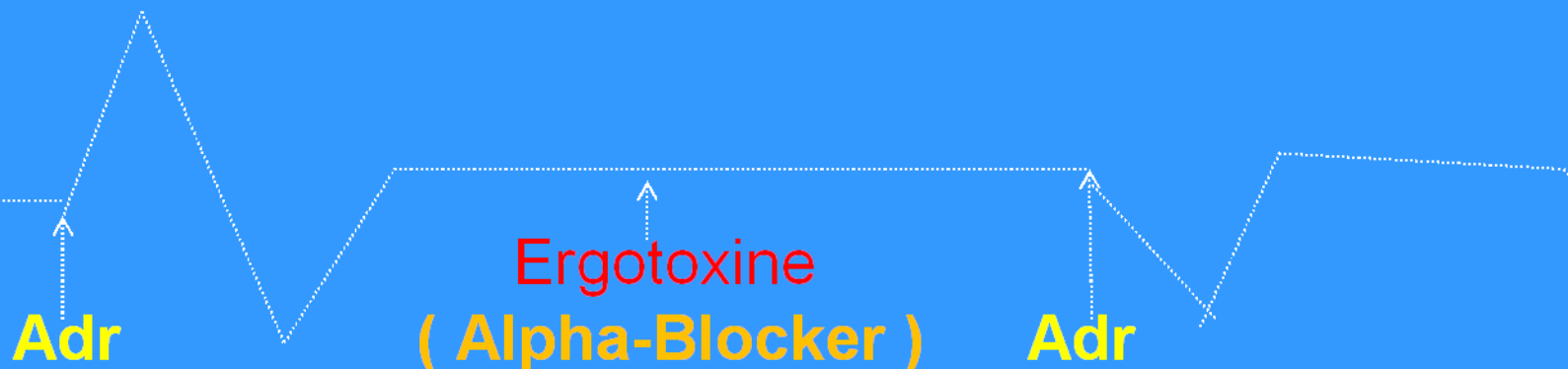
* Silodosin

ALPHA- 2 Antagonist

Eg. * Yohimbine

EFFECTS OF α - BLOCKERS

- 1) $\alpha - 1$ Receptors (Blood vessels):
 - ▶ ↓ Blood Pressure
 - ▶ Postural Hypotension
 - ▶ ↑ Blood volume
 - ▶ Dale's Vasomotor Reversal Phenomenon
- 2) $\alpha - 2$ Receptors (Blood vessels):
 - ▶ ↑ Vasomotor tone, Reflex Tachycardia
 - ▶ Counteracts Hypotensive action



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EFFECTS OF α - BLOCKERS

- (3) Alpha Receptors :-
- Nasal Blood Vessels --- Nasal stuffiness
- Radial Muscles ---- Miosis
- Intestinal Muscles ---- Diarrhoea
- Vas Deferens ---- Inhibit Ejaculation
---- Impotence
- * Bladder ---- Relaxes Sm.Ms of
Bladder & Prostate
---- Improve Urine Flow
Rate

EFFECTS OF α - BLOCKERS

- (3) Alpha - 1 A Receptors :-
 - Detrusor M. of Bladder
 - Trigone of Urinary Bladder
 - Sphincters of Bladder
 - Prostate
- Improves Urine Flow in Patients with Benign Hypertrophy of Prostate (BHP)

EFFECTS OF α - BLOCKERS

- (4) BETA-Adrenoceptors :-
- No effect on Beta-adrenoceptors.
- Therefore,
- No Cardiac stimulation
- No Bronchoconstriction
- No vasodilation

USES OF α - BLOCKERS

- 1) Pheochromocytoma
 - Phenoxybenzamine(PBZ)
 - Phentolamine
- 2) Hypertensive Emergency
 - Phentolamine
- 3) Chronic Hypertension
 - Prazosin
- 4) Persistent Pulmonary Hypertension in New Born
 - Tolazoline
- 5) Secondary Shock
 - Phenoxybenzamine

USES OF α - BLOCKERS

- 6) Peripheral Vascular Disease (PVD)
---- PBZ, Prazosin, Tolazoline
- 7) Extravasation of Noradrenaline
--- Phentolamine
- 8) Benign Prostatic Hypertrophy (BPH)
--- Tamsulosin., Prazosin, Terazosin
- 9) Migraine (Acute Attack)
--- Ergotamine
- 10) Post-Partum Haemorrhage
--- Ergometrine

PHAEOCHROMOCYTOMA

- Tumour of Adrenal Medulla
- ↑ Secretion of NA,Adr. In Blood
- ↑ B.P. sharply (DBP >140 mm Hg)
- DIAGNOSIS :-
- (1) Urinary Estimation of VMA & Normetanephrine (Metabolites of NA,Adr.)
- (2) Phentolamine Test :-
- I.V. 5 mg over 1 min in recumbent subject
- ↓ SBP > 35 mm Hg &/or ↓ DBP > 25 mm Hg
- Indicate Phaeochromocytoma

HYPERTENSION

- Prazosin (α -1 Blocker only)
- Essential Hypertension
- (No reflex Tachycardia)
- Hypertension associated with Dyslipidemia
(\uparrow HDL and \downarrow LDL)
Hypertension associated with BPH
- Non – Selective Blockers not Effective
 - Produces Cardiac stimulation
 - Produces Postural Hypotension
 - Produces Impotence
 - Produces Nasal Blockade.

Phaeochromocytoma (Contd).

- (3) Provocative Test :
- Inj I.V. Histamine/Methacholine/Glucagon
- Promotes release of Catecholamine
- Marked \uparrow BP \rightarrow Phaeochromocytoma
- (Dangerous Test \rightarrow Keep Phentolamine).

TREATMENT OF PHAEOCHROMOCYTOMA

- (1) Phenoxybenzamine – Orally 2-3 wks.
- --- Inoperable or Malignant Tumours
- --- In Surgery (I.V.).
- Shifts fluid from extravascular to vascular compartment
- Normalizes Blood Volume
- Normalizes distribution of body water
- Pre-operative administration prevents action of CA.

BPH (Contd...)

- Static Component



- Treat with
5- α Reductase Inhibitor
(Finasteride)



- Arrest Growth
Neck / Prostate



- ↓ Size of Enlarged
Prostate



- Complete Emptying
of Bladder

- Dynamic Component



- Treat with
 α -1A Adr. Blocker
(Tamsulosin)



- ↓ Tone of Bladder



- ↓ Dynamic Obstruction



- ↑ Urinary Flow Rate

SECONDARY SHOCK

- Due to Blood / Fluid Loss
- Reflex Vasoconstriction
- Extremities - Pale, cold
- Pulse : - Thready and Fast , ↓ Pulse Pressure
- Treatment :- I.V. Phenoxybenzamine



Counteract Vasoconstriction



Improves Tissue Perfusion



Allows Fluid Replacement
(No ↑ Central Venous Pressure (CVP))

SECONDARY SHOCK (Contd..)

- I.V. Phenoxybenzamine



Shift Blood from Pulmonary Circulation



To Systemic Circulation



No Pulmonary Odema on Rapid Fluid Replacement

Peripheral Vascular Disease

- Alpha-Blockers (Prazosin , Tolazoline)
 - * Increase Blood flow to skin & muscle
 - * Effective in Raynaud's Syndrome
(When Vasoconstriction is Prominent)
(Relieves Vasoconstriction, relieves Digital Vasospasm)
 - * Not Effective in PVD like :-
 - Buerger's Disease (Obstruction is organic)
 - Intermittent Claudication (Marked Ischaemia and Vasodilatation)

HYPERTENSION (Contd..)

- Phenoxybenzamine , Phentolamine used :
 - * Rebound Hypertension due to Clonidine withdrawal
 - * Hypertension due to Cheese reaction with MAO – Inhibitors.

HEART FAILURE

- Alpha -1 Blocker – Prazosin
- Affords symptomatic relief in Heart Failure
- Benefit is short lasting due to :-
 - Na⁺⁺ & H₂O retention

MIGRAINE

- Ergotamine (α – blocker)
- Abort / Terminate acute attack of Migraine
- Dose :- 1 mg Half-Hourly . Max. 6 mg/day.

Ergotamine

- ↓
- Stimulates 5-HT_{1D/1B} receptors of Cranial Blood Vessels
- ↓
- Constricts Cranial Blood Vessels
- ↓
- ↓ Shunting of blood from Carotid artery by constricting specific A.V. shunt channels

PRAZOSIN

- Selective $\alpha - 1$ Blocker
- Also blocks $\alpha -1A$, $\alpha -1B$, $\alpha -1D$.
- Absence of $\alpha -2$ blockade (No \uparrow NA release)
- Plasma Half-Life = 2-3 Hrs.
- \downarrow BP, \uparrow HR
- Produces First Dose Phenomenon
(Postural Hypotension, Dizziness, Fainting)
Minimized By :-
 - Giving small dose
 - Dose at Bed Time

USES OF PRAZOSIN

- Antihypertensive drug
- LVF not controlled by Digitalis & Diuretics
- Raynaud's Phenomenon
- Benign Prostatic Hypertrophy
- Tab :- 0.5, 1, 2 mg.
- Dose :- Start with 0.5 mg at bed time, then 1-4 mg twice daily.

TAMSULOSIN / SILODOSIN

- **Uroselective α -1A blocker (Not on α -1B, α -1D receptors)**
- **α -1A \rightarrow Predominant on Bladder & Prostate**
- **α -1B, α -1D \rightarrow Predominant on Blood Vessels**
- **α -1A Blockade \rightarrow \downarrow Tone of Bladder & Prostate Smooth Ms.**
- **\rightarrow \downarrow Dynamic Component of Obstruction**
- **\rightarrow \uparrow Urinary Flow Rate**
- **\rightarrow Complete Emptying of Bladder**
- **α -1B, α -1D \rightarrow \downarrow BP , \uparrow HR (Not seen with Tamsulosin)**
- **No Postural Hypotension , No CVS side effects**
- **Plasma Half – Life = 9 Hrs**
- **Once daily dosing**
- **Better Tolerated**
- **Dizziness as S/E**

PHENOXYBENZAMINE

- Potent Non-selective $\alpha_1 + \alpha_2$ – Adrenoceptor Blocker
- Gradual onset of action
- Prolong effect (3-4 days)
- \downarrow BP (Postural), \uparrow Venous Return, \downarrow TPR
- \uparrow COP, \uparrow Blood flow to organs
- Shifts blood from Pulmonary to Systemic circulation (Due to different action on 2 vascular beds)
- Shifts blood from Extravascular to Vascular compartment (Due to postcapillary dilatation $>$ precapillary vessels)
- Dose ; I.V. 1mg/Kg slow IV infusuin over 1 Hour; Oral : 10-20mg BD
- USES :- (1) Pheochromocytoma
- (2) Secondary Shock
- (3) Peripheral Vascular Disease (PVD).

PHENTOLAMINE

- Potent α -1 & α -2 blocking agent
- ↓ BP (Short acting)
- USES :-
 - (1) Diagnosis & Intraoperative Management of Pheochromocytoma
 - (2) Control Hypertension due to Withdrawal of Clonidine
 - (3) Control Hypertension due to Cheese Reaction with MAOIs
 - (4) To counteract Extravasation of NA / DA during IV use → Given by Local Infiltration; Dose :- 5 mg I.V.
 - (5) As Aphrodisiac in ED in Males → Intracavernosal administration is useful.

SIDE EFFECTS OF α - BLOCKERS

- 1) Postural Hypotension & Syncope
- 2) First Dose Phenomenon (Prazosin)
- 3) Reflex Tachycardia
- 4) Nasal stuffiness
- 5) Miosis ; **Flaccid or Floppy Iris (Tamsulosin/Sildosin).**
- 6) Flushing, Palpitation
- 7) Diarrhoea
- 8) Impotence
- 9) Fluid retention, Angina, MI (Phentolamine, Tolazoline)
- 10) Gangrene of Extremities (Ergot alkaloids)
- 11) Local Tissue Necrosis (INJs.)

BETA- ADRENOCEPTOR BLOCKERS (CLASSIFICATION)

- 1) Non-Selective (B-1 + B2) Antagonists :
 - * Propranolol, Pindolol , Nadolol , Timolol.
- 2) Cardioselective B-1 Antagonists :
 - * Atenolol, Metoprolol, Esmolol, Betaxolol.
- 3) Mixed ($\alpha + \beta$) Antagonists :
 - * Labetolol, Carvedilol
- 4) Beta Antagonists with Intrinsic Sympathomimetic Activity
 - * Pindolol , Oxprenolol, Acebutolol
- 5) Beta Antagonists with Membrane Stabilizing Activity
 - * Propranolol, Pindolol , Metoprolol, Acebutolol, Oxprenolol.
- 6) Beta Antagonists with Intrinsic Sympathomimetic & Membrane Stabilizing Activity:
 - * Oxprenolol, Acebutolol, Pindolol.

Classification of Beta-Adrenoceptors

1) **FIRST GENERATION**

Propranolol, Pindolol (ISA), Timolol, Nadolol, Sotalol

2) **SECOND GENERATION**

Atenolol, Metoprolol, Esmolol, Bisoprolol, Acebutolol (**AMEBA**)

3) **THIRD GENERATION – B-beta Blockers With Additional properties**

(a) **Non-selective B- Blockers with Additional Properties**

Labetolol ($\alpha + \beta$), Carvedilol ($\alpha + \beta$), Bucindolol, Carteolol

(b) **Selective B -1 Blockers with Additional Properties**

Celiprolol (**Vasodilator**), Nebivolol, Betaxolol

Third Generation B- Blockers With Vasodilator Mechanism

1. **Direct Action** :- Celiprolol
2. **Alpha – Blocker** – Labetalol, Carvedilol
3. **B-2 Agonism** – Celiprolol, Carteolol
4. **Nitric Oxide (NO) Production** - Celiprolol, Nebivolol
5. **Ca²⁺ - Channel blocker** – Carvedilol, Betaxolol
6. **K⁺- Channel Opener** – Tilisolol
7. **Antioxidant** - Carvedilol

Significance of B-1 Cardioselectivity

Ex. Atenolol, Metoprolol

Advantages :-

- 1) Preferred in patients with Bronchial Asthma, DM, PVD.
 - 2) Less likely to impair Exercise capacity
 - 3) No ↓ in HDL – Level or ↑ in TGs level

Disadvantages

- 1) Not useful in tremors, anxiety, migraine
- 2) Block Tachycardia.. Warning sign of hypoglycaemia
- 3) Do not protect cardiac cells from catecholamines excess & Hypokalemia
- 4) Not useful in Hyperthyroidism - Does not inhibit peripheral conversion of T4 into T3. No relief in tremors.

Significance of B-Blockers With Partial Agonist / Intrinsic Sympathomimetic Action

Ex. Celiprolol, Pindolol, Acebutolol

Advantages

- 1) Safe in elderly Pts with Bradycardia, Sick sinus Syndrome or with Low Cardiac Reserve.
- 2) Safe in Asthmatic Pts – No Bronchoconstriction
- 3) No withdrawal symptoms - Rebound Hypertension or Angina
- 4) No alteration in Plasma Lipid Profile
- 5) No Supersensitivity

Disadvantages

- 1) Not suitable for prophylaxis of Myocardial Infarction (MI)
- 2) Not effective in Migraine Prophylaxis – dilates cerebral Blood Vessels

Significance of B-Blockers with Membrane Stabilising or Local Anaesthetic (LA) property

Ex. Propranolol, Acebutolol, Oxprenolol

Advantages

- 1) Possess Local anaesthetic Action
- 2) Hence, Used as Antiarrhythmic Drugs at Higher Doses

Disadvantages

- 1) If used topically causes ocular local anaesthesia which is undesirable
- 2) Timolol & Betaxolol used topically in Glaucoma – Devoid of Local Anaesthetic activity.

Significance of B-Blocker With Alpha- Receptor Blocking Action

Ex. Carvedilol, Labetalol

1) Produces Vasodilatation

2) Reduction in PVR & After load

3) Fall in Blood Pressure

4) Useful I Treatment of Hypertension & Cardiac Failure

Significance of B- Blockers with lipid solubility

EX. Propranolol, Metoprolol

- 1) **Crosses Blood Brain Barrier (BBB)**
- 2) **Produces CNS side Effects – Sedation / Sleep Disturbances / Night Mares (Vivid dreams).**
- 3) **Excreted in urine**
- 4) **Atenolol, Nadolol** are lipid insoluble-do not cross BBB-
No CNS side effects
- 5) **Atenolol, Nadolol** being lipid insoluble are excreted unchanged in urine & are long acting.

ACTIONS OF BETA- ADRENOCEPTOR BLOCKERS

- Blocks Beta-adrenoceptors
- Blockade is competitive & reversible
- ↓ cAMP Production.
- **HEART :**
- **Anti-anginal Effect**
 - * -ve Inotropic effect
 - * -ve Chronotropic effect , ↓ C.O., ↓ PVR
 - * ↓ Cardiac work load
 - * ↓ Oxygen demand,
 - * Improves Exercise Tolerance

ACTIONS OF BETA- ADRENOCEPTOR BLOCKERS

- **HEART :**
- **Anti-arrhythmic Effect :-**
 - ↓ in Automaticity of Ectopic pacemaker
 - ↓ in Conduction through A.V. node.
 - ↑ Refractory Time of AV Node (Prolongs P-R Interval)
 - ↑ Conduction time, Delayed AV conduction

(Common with B-Blockers with Membrane-Stabilizing /LA activity / Quinidine – like Effect).

ACTIONS OF BETA- ADRENOCEPTOR BLOCKERS

- **BLOOD PRESSURE :-**
- **(a) Heart :- Blocks B-1 Receptors on Heart**
 - ↓ B.P. in Hypertensives (Not in Normotensives) due to :-
 - * ↓ in H.R., ↓C.O.P., ↓Renin and N.A. release, ↓**T.P.R.**
- **(b) Kidneys :- Blocks B-1 Receptors on Kidneys**
 - ↓ Pl. Renin Activity, ↓ Blood Volume, ↓ B.P.
 - ↓ Aldosterone secretion, ↑ Na ++ & H₂O Excretion, ↓ B.P.
- **(c) Additional Actions :-**
 - Direct Vasodilator Property (**Celiprolol**)
 - Additional α - Blocking action (**Labetalol, Celiprolol**)
 - Partial Agonist Action on B – receptors (**Pindolol**)
- **RESPIRATORY TRACT :**
 - * *Bronchospasm (Propranolol blocks B-2 receptors)*
 - * *↑ Airway Resistance in Bronchial Asthmatic patients*

ACTIONS OF BETA- ADRENOCEPTOR BLOCKERS

- **METABOLIC :**

- * Inhibits Lipolysis
- * Inhibits Glycogenolysis (B-2 receptors in Liver)
- * Propranolol causes Hypoglycaemia
- * Propranolol Augments Hypoglycaemia in Diabetic Patients on Insulin or Oral Hypoglycemic Therapy
- * Propranolol Masks antidiabetic drugs - induced Hypoglycaemic symptoms like Palpitation, Tachycardia, Nervousness, Perspiration → Leading to Hypoglycaemic coma with further doses of antidiabetic drugs in presence of B-blockers. Hence, Propranolol is C/I in Diabetic Patients.

ACTIONS OF BETA- ADRENOCEPTOR BLOCKERS

- **ENDOCRINE:**

- Impairment from recovery from hypoglycemia
- ↑ VLDL, Cholesterol
- ↓ HDL, HDL / LDL ratio → ↑ risk of CAD.

(Less changes in Lipid Profile with ISA –β-blockers).

- **OTHERS:**

- * ↓ Anxiety, Apprehension, Tremors, Palpitation
*(Hence, **Propranolol is used Prophylactically**).*

- **EYES:**

- ↓ Production/Secretion of Aqueous Humour
- ↓ Intraocular Pressure (IOP) eg. Timolol, Betaxolol.
- **Levobetaxolol** has **Neuroprotective effect** on retinal neurons by blocking ganglionic cell death in Glaucoma by attenuating Ca^{++} & Na^{+} influx.

USES OF BETA- ADRENOCEPTOR BLOCKERS

1) Cardiovascular Diseases :-

- A) Hypertension : Alone or with Diuretics.
- B) Ischaemic Heart Disease :-
 - * ↓ Frequency of anginal attacks
 - * Improves Exercise tolerance in anginal Pts.
- C) Myocardial Infarction (MI) :-
 - * ↓ Infarct size in acute attack.
 - * ↓ ReInfarct rate on chronic use

USES OF BETA- ADRENOCEPTOR BLOCKERS

D) Cardiac Arrhythmias :-

- * *Supraventricular Tachycardia*
 - * *Atrial Flutter*
 - * *Atrial Fibrillation*
- (They reduce ventricular rates).*

E) Obstructive Cardiomyopathy :-

F) Dissecting Aortic Aneurysm :-

USES OF BETA- ADRENOCEPTOR BLOCKERS

2) Eye Disorder :-

A) Chronic Open (Wide) Angle Glaucoma :-

- * ↓ Intra Ocular Pressure (IOP) by decreasing formation/production of *Aqueous Humour*.
(*Timolol, Betaxolol, Levobutonolol*).

3) Endocrinal Disorder :-

A) Hyperthyroidism :-

- * Blocks Beta-receptors mediated anxiety, palpitation, tachycardia.
- * Prevents conversion of T4 (Thyroxine) into T3 (Thyronine).

B) Phaechromocytoma :-

- * Along with Alpha – blockers.

USES OF BETA-ADRENOCEPTOR BLOCKERS

4) Neurological Diseases :-

A) Migraine :- (Prophylaxis/Prevention) Eg. Propranolol.

* ↓ Frequency and Intensity of Attack.

B) **Somatic Manifestations of Anxiety, Apprehension, Tremors & Palpitation** occurring during examinations, Public Speaking (Propranolol is used Prophylactically).

C) **Alcohol Withdrawal Symptoms.**

5) Others :-

A) **Chronic Alcoholic with Liver Cirrhosis (I.V. Propranolol)**

* ↓ Portal Venous Pressure, thereby prevent Haemetemesis from ruptured esophageal blood vessels.

ADVERSE EFFECTS OF BETA-ADRENOCEPTOR BLOCKERS

- 1) CVS :-

- * CHF in susceptible patients.
- * Cold Extremities (↓ in Blood flow)
- * Worsens Peripheral Vascular Disease (PVD)
- * Sudden Stoppage results into :-
- * Rebound Hypertension
- * Precipitates Angina / MI
- * Life Threatening ↑ in Airway resistance in Bronchial asthmatic Patients (Bronchospasm).

ADVERSE EFFECTS OF BETA-ADRENOCEPTOR BLOCKERS

- 2) RESPIRATORY SYSTEM :-
 - * Life Threatening \uparrow in Airway resistance in Bronchial asthmatic Patients (Bronchospasm).
- 3) ALLERGIC REACTIONS :-
 - * Thrombocytopenia
 - * Agranulocytosis
- 4) CNS :-
 - * *Muscles Cramps* * *Insomnia* * *Nightmares* * *Depression*
- 5) METABOLISM :-
 - * *Blunting of recognition of Hypoglycaemia*
 - * *Delay in recovery from Insulin induced Hypoglycaemia.*

THANK YOU....

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