Medical Committee
The University of Jordan

PHARMACOLOGY

Slide # : 12-Adrenoceptor Antagonists

SHEET

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SLIDES

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Adrenoceptor Antagonists

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Adrenoceptor Antagonists

1. **α-Adrenoceptor Antagonists.**
2. **β-Adrenoceptor Antagonists.**

α-Adrenoceptor Antagonists

1. **Reversible antagonists dissociate from the receptor, and the block can be overcome by sufficiently high concentration of the agonist. In this case the duration of action is largely related to the t½ of the drug.**

   e. g: Prazosin, Tamsulosin, Phentolamine.

α-Adrenoceptor Antagonists

2. **Irreversible antagonists do not dissociate from the receptor and their block can not be overcome by the agonist. They bind covalently to the receptor (ethyleneimonium intermediate).**

α-Adrenoceptor Antagonists

The effect of an irreversible antagonist may persist long after the drug has been cleared from the plasma.

- **The restoration of α responsive is dependent on the synthesis of new α-receptor.**

  e. g: phenoxybenzamine.

α-Adrenoceptor Antagonists

Pharmacodynamics:

A. **Cardiovascular system:**

Block of α_1-receptors in arterioles leads to vasodilation, lowering of peripheral vascular resistance and blood pressure.

Block of α_1-receptors in venules leads to venodilation, postural hypotension and reflex tachycardia.

α-Adrenoceptor Antagonists

- **Tachycardia is more marked with nonselective α-blockers (α_1, α_2) because of increased release of norepinephrine (why?).**

α-Adrenoceptor Antagonists

B. Other effects:

- **Miosis (α_1 receptors in dilator pupillae).**
- **Nasal stuffiness (α_1 receptors in blood vessels).**
- **Decreased resistance to the outflow of urine (α_1 receptors in the base of urinary bladder and the prostate).**

Phentolamine

- **Is a potent competitive antagonist at both α_1 and α_2 receptors equally.**
- **It causes reduction of peripheral resistance through blockade of α_1 receptors.**
- **Cardiac stimulation is through baroreflex mechanisms as well as due to block of presynaptic α_2 receptors → which enhances norepinephrine release.**

Phentolamine

- **It has minor inhibitory effect at serotonin receptors.**
- **It has agonist effect at muscarinic and H_1 and H_2 histamine receptors.**
- **It has poor absorption after oral administration.**

Phentolamine

- **Adverse effects are related to cardiac stimulation (tachycardia, arrhythmias and myocardial ischemia).**
- **Other adverse effects include nasal congestion and headache.**
- **Used mainly for hypertension of pheochromocytoma.**

Phenoxybenzamine

- **More effective at α_1 than α_2 receptors.**
- **It may also inhibit the reuptake of released norepinephrine by presynaptic adrenergic nerve terminals.**
- **It also blocks histamine H_1 receptors, cholinergic and serotonin receptors as well.**
- **The pharmacologic actions are similar to phentolamine.**

Phenoxybenzamine

- **Absorbed after oral administration but bioavailability is low.**
- **Adverse effects include tachycardia, postural hypotension, nasal stuffiness and inhibition of ejaculation.**
- **Because it enters the CNS it may produce fatigue, sedation and nausea.**
- **The major use is in the treatment of pheochromocytoma.**

Prazosin

- **It is highly selective for α_1 receptors and typically 1000-fold less potent at α_2 receptors.**
- **Thus, it produces less tachycardia than phentolamine and phenoxybenzamine (why?).**
- **Relaxes smooth muscle in arterioles, venules and prostate (α_1).**
- **Extensively metabolized, t½ ~ 3 hours.**
- **It is effective in the management of hypertension.**

Terazosin

- **Is also α_1-selective antagonist.**
- **Effective in hypertension.**
- **Also used in patients with benign prostatic hyperplasia with urinary symptoms.**
- **It is extensively metabolized.**
- **The t½ ~ 9-12 hours.**
- **Doxazosin, Tamsulosin, Alfuzosin, Indoramin are similar.**

α-Adrenoceptor Antagonists

Therapeutic uses:

1. **Pheochromocytoma.**
2. **Hypertensive emergencies.**
3. **Chronic hypertension.**
4. **Antidote for local vasoconstrictor excess due to infiltration of α agonists.**
5. **Urinary obstruction due to benign prostatic hyperplasia.**

β-Adrenoceptor Antagonists

- **These drugs occupy β receptors and competitively inhibit occupation of these receptors by catecholamines.**
- **Most of them are pure antagonists – cause no activation. e. g: Atenolol, Bisoprolol, Carvedilol, Esmolol, Metoprolol, Nadolol, Propranolol, Sotalol, Timolol.**

β-Adrenoceptor Antagonists

- **Some are partial agonists – they cause partial activation of the receptor in the absence of the full agonist. e. g: Acebutolol, Labetolol, Pindolol.**
- **Relative affinity to β_1 and β_2 receptors: some of the antagonists have higher affinity for β_1 than β_2 receptors. This selectivity is not absolute. It is dose related and tend to diminish at higher concentration.**

β-Adrenoceptor Antagonists

- **e. g: Acebutolol, Atenolol, Bisoprolol, Esmolol, Metoprolol.**

Pharmacokinetics:

- **Most of these drugs are well absorbed after oral administration.**

β-Adrenoceptor Antagonists

- **Propranolol undergoes extensive hepatic first-pass metabolism → low bioavailability → oral dose is much larger than IV dose. Because first-pass effect varies among individuals, there is great interindividual variability in the plasma concentration after oral propranolol.**

β-Adrenoceptor Antagonists

- **Its elimination is reduced in the presence of liver disease, reduced hepatic blood flow and in the presence of enzyme inhibitors. It crosses the BBB.**
- **Metoprolol is also metabolized in the liver. The CYP2D6 genotype is the major determinant of its clearance (PMs have 3-10 fold plasma concentration than EMs).**

β-Adrenoceptor Antagonists

- **Pindolol and sotalol bioavailability is better.**
- **Atenolol and nadolol are mainly excreted unchanged in urine. Their half life is prolonged in renal failure.**

β-Adrenoceptor Antagonists

- **t½:**

Acebutalol,	
Metoprolol,	
Pindolol	**3-4 hours**
Atenolol	**6-9 hours**
Bisoprolol	**9-12 hours**
Carvedilol	**7-10 hours**
Esmolol	**10 minutes (rapidly hydrolyzed)**
Labetalol	**5 hours**
Nadolol	**14-24 hours**
Propranolol	**3-6 hours**
Sotalol	**12 hours**
Timolol	**4-5 hours**

β-Adrenoceptor Antagonists

Pharmacodynamics:

A. Effects on the cardiovascular system:

1. Lowering of blood pressure in patients with hypertension, despite of block of β_2 receptors. The mechanism is probably multifactorial and may involve:

β-Adrenoceptor Antagonists

i. Negative inotropic effect on the heart → reduction of cardiac output.

ii. Suppression of renin-angiotensin system.

iii. A centrally-mediated effect due to reduction of sympathetic outflow from the CNS.

β-Adrenoceptor Antagonists

2. Negative chronotropic effect → bradycardia.

3. Slowing of AV nodal conduction and prolonging its refractory period. This is useful for treating supraventricular arrhythmias.

4. Conventional doses do not usually produce hypotension in healthy individuals with normal blood pressure.

β-Adrenoceptor Antagonists

B. Effects on respiratory tract:

Increased airway resistance due to block of β_2 receptors. In bronchial asthma it is preferable to use selective β_1 receptor blockers if they are needed for other conditions.

C. Effects on the eye:

Reduce intraocular pressure (useful for glaucoma) due to reduction in aqueous humor production.

β-Adrenoceptor Antagonists

D. Metabolic and endocrine effects:

1. Inhibition of lipolysis (β_3).

2. Partial inhibition of glycogenolysis (β_2).

3. Impair recovery from hypoglycemia in insulin-dependent diabetic patients. β_1 receptor antagonists are less prone to do so.

β-Adrenoceptor Antagonists

- **These drugs are safer in type 2 diabetics who do not usually have frequent hypoglycemic episodes.**

4. Chronic use has been associated with increased plasma concentrations of VLDL and decreased concentration of HDL→ atherosclerosis → increased risk of coronary artery disease. This is less common with partial agonists. Mechanism is unknown.

β-Adrenoceptor Antagonists

E. Effects not related to β-blockade:

Local anesthetic action or membrane-stabilizing action is a prominent effect of several β-blockers, due to sodium channel blockade but at concentrations higher than those achieved during therapy.

Propranolol

- **It is the prototypical β-blocker.**
- **It is non-selective agent.**
- **It has a low and dose-dependent bioavailability.**

Metoprolol, Atenolol

- **Are β_1-selective.**
- **Are safer in patients who experience bronchoconstriction with propranolol.**
- **May be preferable for myocardial infarction in patients having diabetes, peripheral vascular disease, chronic obstructive pulmonary disease.**

Nadolol

- **Is peculiar in its long duration of action.**

Timolol

- **It has excellent ocular hypotensive effect when used topically in the eye.**

Pindolol, Acebutolol, Oxprenlol

- **Have partial β-agonist activity**
- **Less likely to cause bradycardia and abnormalities in plasma lipids.**

Labetalol

- **Is available as racemic mixture of two pairs of chiral isomers.**
- **The (S,S)- and (R,S)- isomers are inactive.**
- **The (S,R)- isomer is a potent α_1-selective blocker.**
- **The (R,R)- isomer is a potent β-blocker.**
- **Reduces blood pressure with less reflex tachycardia than phentolamine (why?).**

Carvedilol

- **It is a nonselective β-receptor antagonist with some capacity to block α_1-adrenergic receptors.**
- **It is extensively metabolized in the liver partially by the polymorphic CYP2D6 enzyme → drug-drug interactions.**
- **t½ ~ 6-8 hours.**

Carvedilol

- **It attenuates oxygen free radical-initiated lipid peroxidation.**
- **It inhibits vascular smooth muscle mitogenesis. (the last 2 are important for its use in the treatment of chronic heart failure).**

Esmolol

- **It is an ultra-short-acting β_1-selective adrenoceptor antagonist.**
- **It is rapidly inactivated by red blood cells esterases. ($t_{½}$ ~ 10 min).**
- **It is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis and myocardial ischemia in acutely ill patients (why?).**

β-Adrenoceptor Antagonists

Therapeutic Uses:

1. **Hypertension.**
2. **Ischemic heart disease: Reduce cardiac work and oxygen demand (negative inotropic and chronotropic effect).**
3. **Supraventricular (and ventricular) cardiac arrhythmias:**

β-Adrenoceptor Antagonists

A. They slow ventricular response rate in patients with atrial fibrillation or flutter due to reduction in AV nodal conduction velocity and an increase refractory period.

B. They reduce ventricular ectopic beats precipitated by catecholamines.

C. Sotalol has additional antiarryhthmic effect (will be discussed with CVS).

β-Adrenoceptor Antagonists

4. **Heart failure (??): Three β-antagonists have been proved to be useful in chronic heart failure (metoprolol, bisoprolol & carvedilol). These drugs may worsen acute congestive heart failure, requiring careful and gradual dose increments.**

β-Adrenoceptor Antagonists

5. **Glaucoma (timolol).**
6. **Hyperthyroidism: To combat the excessive sympathomimetic activity associated with this condition (propranolol).**
7. **Prevention of migraine headache (reduce frequency and intensity).**

β-Adrenoceptor Antagonists

8. **Treatment of anxiety and tremors associated with sympathetic overactivity (propranolol).**
9. **Reduction of portal vein pressure in patients with hepatic cirrhosis (propranolol and nadolol).**

β-Adrenoceptor Antagonists

Adverse Effects:

1. **Drug allergy**
2. **Sedation, sleep disturbances, depression, psychotic reactions, nightmares – propranolol (CNS).**
3. **Worsening of bronchial asthma ← bronchoconstriction (β_2).**

β-Adrenoceptor Antagonists

4. **Worsening of peripheral vascular disease and vasospastic conditions (β_2).**
5. **Reduction of cardiac output and cardiac decompensation → heart failure.**
6. **Bradycardia.**
7. **Atrioventricular block and cardiac arrest.**

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7. **Masking the symptoms of, and delaying recovery from, hypoglycemia in diabetic patients taking insulin (β_2).**

β-Adrenoceptor Antagonists

9. **Withdrawal syndrome: Abrupt discontinuation of these drugs leads to rebound effects (exaggeration of the condition they were used to treat) because of upregulation (increased number) of receptors during treatment. Therefore, when these drugs are to be discontinued, tapering of the dose (gradual reduction) rather than sudden withdrawal is recommended.**