Class 2: Alpha and Beta Blockers – Antiarrhythmic Drugs

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In this article, we will study the important pharmacological aspects of alpha and beta blockers such as classification, pharmacokinetics, mechanism of action, important actions on various organ systems, clinical uses and toxicity.

Definition of Alpha and Beta Blockers

**Alpha blockers** generally help relax the muscles, which in turn can lead to the opening of the blood vessels for smooth circulation. The Beta Blockers, on the other hand, work by reducing the person's heart rate. Thus, it results in the reduction of blood flow. The BP is decreased because of the dilation of the blood vessels. Alpha Medications work by keeping the hormones of norepinephrine or noradrenaline at bay. Thus, it can lead to a smoother blood flow through open veins.

**Beta Blockers**, meanwhile, works by blocking the hormone called epinephrine or better known as adrenaline. This hormone often causes increased heart rates that can lead to increased blood pressure levels. The Beta medication prevents this from happening. Alpha blockers simply work to lower blood pressure and increase the blood flow to the heart while the Beta medications work in slowing the heart rate at the same time lowering BP rates.
Classification of Alpha and Beta Blockers

Adrenoceptor blockers are classified based upon their selectivity towards adrenoreceptors.

**Alpha blockers**

- **Non-selective**: phenoxybenzamine, phentolamine
- **$\alpha_1$-selective**: prazosin, terazosin, doxazosin, alfuzosin, indoramin, urapidil, bunazosin, tamsulosin
- **$\alpha_2$-selective**: yohimbine

<table>
<thead>
<tr>
<th>$\alpha$-Methyldopa (Aldomet®)</th>
<th>Clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease central sympathetic outflow</td>
<td>Decrease central sympathetic outflow</td>
</tr>
<tr>
<td>Prodrug; metabolized to methylnorepinephrine</td>
<td></td>
</tr>
<tr>
<td>Decreases central sympathetic outflow, cardiac output, and vascular resistance</td>
<td>Decreases central sympathetic outflow, cardiac output, and vascular resistance</td>
</tr>
<tr>
<td>Compensatory reaction: salt retention</td>
<td>Compensatory reaction: salt retention</td>
</tr>
</tbody>
</table>
| **Idiosyncratic reaction:**  
  - Hematologic immunotoxicity (positive Coombs test) \(\rightarrow\) hemolytic anemia  
  - Sedation | **Idiosyncratic reaction:**  
  - Rebound hypertension if discontinued (restart it, or use phentolamine, an alpha blocker)  
  - Sedation |
| Previously used extensively for pregnancy; second most common | **Not** used in pregnancy |

**Beta Blockers**
- **Non-selective**: nadolol, penbutolol, pindolol, propranolol, timolol, sotalol, metoprolol, carteolol, carvedilol*, labetalol*

- **β₁-selective**: acebutolol, atenolol, bisoprolol, esmolol, metoprolol, betaxolol, nebivolol

- **β₂-selective**: butoxamine

<table>
<thead>
<tr>
<th>Notable β-Blocker</th>
<th>Metropolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranol</td>
<td>• Prototypical β-blocker</td>
</tr>
<tr>
<td></td>
<td>• Short-acting, poor BP control</td>
</tr>
<tr>
<td></td>
<td>• Used in anxiety and stage fright also</td>
</tr>
<tr>
<td></td>
<td>• Can be used to fool a lie detector test!</td>
</tr>
<tr>
<td>Labetalol</td>
<td>• Nonselective third generation</td>
</tr>
<tr>
<td></td>
<td>• Wide therapeutic margin (200—2400 mg/day)</td>
</tr>
<tr>
<td></td>
<td>• Excellent BP control</td>
</tr>
<tr>
<td></td>
<td>• Most used BP med in pregnancy</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>• Once daily β-blocker</td>
</tr>
<tr>
<td></td>
<td>• More β₁ selective, used post-MI</td>
</tr>
<tr>
<td></td>
<td>• Good BP control</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-Blockers with additional activity</th>
<th>Carvedilol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebivolol</td>
<td>• “Novel” third generation selective β-blocker</td>
</tr>
<tr>
<td></td>
<td>• β₁ selective</td>
</tr>
<tr>
<td></td>
<td>• Also, has nitric oxide activity — direct vasodilator</td>
</tr>
<tr>
<td></td>
<td>• Excellent BP control</td>
</tr>
<tr>
<td></td>
<td>• Caution: Endothelial dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Nonselective third generation β-blocker</td>
</tr>
<tr>
<td></td>
<td>• Also, has alpha activity</td>
</tr>
<tr>
<td></td>
<td>• Used in heart failure</td>
</tr>
<tr>
<td></td>
<td>• Poor BP control</td>
</tr>
</tbody>
</table>

**Mnemonics to remember this classification:**

α-blockers generally end with **-in**.

β-blockers generally end with **-olol**.

**Important:**

- Phenoxybenzamine is a long-acting irreversible α-blocker.
- Phentolamine is a short-acting reversible α-blocker.
- *Carvedilol and labetalol also block α-receptors.

**Always remember:** In the sympathetic nervous system, the transmitter in effector organs is **norepinephrine**, while, in the parasympathetic nervous system, the transmitter in effector organs is **acetylcholine (Ach)**. Alpha and beta blockers have an
 antagonistic action on the sympathetic nervous system.

Adrenoceptors – Alpha and Beta Receptors

**α1 Receptors**
- Located at GI tract and bladder sphincter, vascular smooth muscles of skin and splanchnic regions, and radial muscle of iris.
- Function: generally produce smooth muscle constriction.
- Mechanism of action: they act via stimulation of IP$_3$/Ca$^{2+}$

**α2 Receptors**
- Present in presynaptic nerve terminals, platelets, fat cells and the wall of the GI tract.
- Function: generally produce relaxation/dilation.
- Mechanism of action: they act via inhibition of adenylate cyclase and decreasing the concentration of cAMP (cyclic adenosine monophosphate).

**β1 Receptors**
- Located on heart SA, AV node, atrial and ventricular muscle, His-Purkinje, and kidney.
- Mechanism of action: they act via stimulation of adenylate cyclase and decreasing the concentration of cAMP (cyclic adenosine monophosphate).

**β2 Receptors**
- Located on smooth vessels of skeletal muscle, blood vessels, GIT, uterus, liver and urinary tract.
- Mechanism of action: they act via stimulation of adenylate cyclase and decreasing the concentration of cAMP (cyclic adenosine monophosphate).

Effect of Adrenoceptors on Organ Systems

It is suggested to first learn and memorize the action of alpha and beta receptors on various organ systems. If the action of alpha and beta receptors is known, then it is easy to remember the effect of alpha and beta blockers on those organ systems because they have the opposite actions to the alpha/beta agonists.

<table>
<thead>
<tr>
<th>Receptor/organ system</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α1 receptors</strong></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>Contraction (mydriasis) of the iris dilator muscle.</td>
</tr>
<tr>
<td>Bladder</td>
<td>Constriction of bladder sphincter, Control of micturition and urine flow. Note: α-blockers increase the urine flow by promoting the relaxation of the bladder muscles.</td>
</tr>
<tr>
<td>Prostate</td>
<td>Cause ejaculation by prostate contraction. α-blockers are used to treat benign prostatic hyperplasia (BPH) induced urinary obstructions because it causes the relaxation of the bladder muscles (the opposite actions to the alpha agonists). α-blockers also produce impaired ejaculation due to their α-receptor antagonism.</td>
</tr>
<tr>
<td>Kidney</td>
<td>Decrease renin secretion.</td>
</tr>
<tr>
<td>Veins and arterioles (skin)</td>
<td>Contraction of smooth muscles of the peripheral blood vessels.</td>
</tr>
<tr>
<td>α2 receptors</td>
<td>Increase the platelet aggregability.</td>
</tr>
<tr>
<td>β1 receptors</td>
<td>Increase heart rate, conduction velocity, contractibility and AV node conduction.</td>
</tr>
<tr>
<td>β2 receptors</td>
<td>Promote dilation of arterioles and veins. Consequently a decrease in TPR, BP, afterload. Beta blockers are used in the treatment of hypertension.</td>
</tr>
<tr>
<td>Veins and arterioles</td>
<td>In contrast to the receptors, these stimulate bladder relaxation. No effect on the ejaculation.</td>
</tr>
<tr>
<td>Bladder</td>
<td>Bronchiolar smooth muscle relaxation</td>
</tr>
<tr>
<td>Kidney</td>
<td>Increase the renin secretion</td>
</tr>
<tr>
<td>Liver</td>
<td>Increased glycogenolysis</td>
</tr>
</tbody>
</table>

**Alpha Adrenergic Blocking Agents**

These drugs block the action of alpha-adrenoceptors. They are commonly used in the treatment/management of **hypertension**, and **benign prostatic hyperplasia** (BPH).

**Phenoxybenzamine** and **phentolamine** are two non-selective alpha-adrenergic blocking agents. Thus, they act at both α1 and α2 receptors.

**Phenoxybenzamine** binds covalently with the adrenergic receptors (irreversible and non-competitive). Due to irreversible binding, phenoxybenzamine has a longer duration of action. It decreases the BP by the prevention of the **constriction of the peripheral blood vessels**. However, due to increased cardiac output, it doesn’t cause a prolonged drop in BP, thus it is not widely used for this purpose.

**Phentolamine** is a reversible and competitive type of alpha-adrenergic blocking agents. It has a shorter duration of action and it is used in the treatment of **pheochromocytoma**.

**Prazosin, terazosin, doxazosin**, and **tamsulosin** have selective antagonistic action on α1 receptors.

**Prazosin**: It has 1000 times more selectivity action on α1 receptors. Due to selectivity in action, a marked **orthostatic hypotension** and **tachycardia** are generally observed with non-selective alpha-adrenergic blocking agents such as phenoxybenzamine and phentolamine are comparatively less with α1 selective alpha blockers.

Prazosin is an important drug in the **treatment of hypertension** and BPH. Terazosin and doxazosin have similar actions. Terazosin (80%) has a **higher bioavailability** than prazosin (50%).

**Tamsulosin**: Postural hypotension is not observed with this drug.

**Yohimbine**: Before the discovery of phosphodiesterase-5-inhibitors such as sildenafil, it was used to treat impotence (ED) in men, but, nowadays, it is not used for the treatment of ED due to the availability of more safer and effective alternatives.

**Please note**: Alpha blockers (both selective and non-selective) are not recommended as monotherapy in hypertension due to the availability of other effective **anti-hypertensives**.
Adverse Effects of Alpha Adrenergic Blocking Agents

Adverse effects of alpha blockers are mainly due to their antagonistic action/blocking effects of α receptors.

- **Orthostatic hypotension**: This results due to the pooling of blood in the veins of the legs. Fainting can also result due to the reduced supply of blood to the brain. It is the most common side-effect with alpha blockers. It is more marked with the use of non-selective alpha blockers and less marked with the use of α1 selective blockers.
- Dizziness and headache.
- **Reflex tachycardia**: Increased heart rate due to the stimulation of baroreceptors.
- Drowsiness.
- **Nasal stiffness** due to alpha receptor blockage.
- Since alpha receptors have a role in the contraction of smooth muscle of prostate which induces ejaculation in males, blockage of alpha receptors inhibits the ejaculation process in males.

Beta-Adrenergic Blocking Agents

All the beta blockers or beta-adrenoceptor blockers antagonize the action of beta receptors.

A simple trick to remember the actions of beta blockers on various organ systems is to first memorize the action of beta-agonists on the organ system. Beta blockers always have an opposite action on organ systems to the beta agonist.

**Always remember**: cardioselective β-blockers (atenolol, metoprolol, acebutolol, esmolol, bisoprolol, betaxolol) have a selective action on β1 receptors.

**The advantage of cardioselective β-blockers**: They are safer in asthma (don’t cause bronchoconstriction), diabetes, and peripheral vascular disease.

**Important**: Beta blockers do not cause postural hypotension as they don’t have any action on α receptors.

Beta blockers act by reducing the **cardiac output** (volume of blood pumped by the heart per minute); thus, a decrease in the volume of blood pumped from the heart also reduces the BP.

**Pharmacological Actions of Propranolol (Prototype Drug)**

Propranolol is described as a prototype drug here. It is a non-selective beta blocker. Important indications and side effects of other beta blockers will be discussed in the next sections.

**Effects of Beta-Adrenergic Blocking Agents**

**Effect on Cardiovascular System**

- ↓ cardiac output
- ↓ heart rate (produce bradycardia)
- ↓ force of contraction
- ↓ total peripheral resistance (TPR)
- Negative chronotropic and inotropic actions
  - also decrease the renin release from the kidneys, which is thought to be their mechanism of action in reducing the BP

**Always remember:**

Action by beta blockers on β2 receptors is considered as undesired because non-selective beta blockers cause bronchoconstriction, decrease insulin secretion and glycogenolysis.

**Cardioselective beta blockers** always act on β1 receptors.

**Effect on Pulmonary System**

Non-selective beta blockers such as propranolol can produce bronchoconstriction or can exacerbate asthma in asthmatics.

Due to this, propranolol should be avoided in asthmatics and patients suffering from COPD.

**Always remember:** Beta blockers always show effects opposite to beta agonists.

β1 agonists such as salmeterol and salbutamol have a bronchodilatory effect on the lungs.

**Effects on the Eyes**

![Image: Photograph showing acute angle-closure glaucoma which is a sudden elevation in intraocular pressure that occurs when the iris blocks the eye’s drainage channel—the trabecular meshwork.” by Jonathan Trobe, M.D. - The Eyes Have It. License: CC-BY 3.0](image)

Beta blockers reduce the intraocular pressure. Thus, they are used to treat glaucoma. They also reduce the production of aqueous humor in the eyes (timolol).

**Metabolic effects**

They increase the levels of insulin in the body – if a beta blocker is given to a diabetic patient who is on insulin therapy, there could be a drastic hypotension. Thus, beta blockers are contraindicated in diabetes.

Beta-blockers also block glycogenolysis and gluconeogenesis.
Clinical uses of beta-adrenergic blocking agents

- **Hypertension** (carvedilol, labetalol, propranolol)
- **Angina pectoris** (propranolol)
- **Myocardial infarction** (propranolol and esmolol)
- Glaucoma (timolol, betaxolol, carteolol – applied topically)
- **Migraine** (propranolol)
- Performance anxiety (propranolol)
- **Hyperthyroidism** (propranolol)

Adverse effects and toxicity of beta blockers

- **Bradycardia**
- **AV blockage**
  - Severe asthma attacks (propranolol)
- **Hypoglycemia**
  - **Arrhythmias** (upon abrupt stoppage of therapy with beta blockers)
- **Sexual dysfunction** (propranolol)
- **Fatigue**
- **Vivid dreams** (propranolol)

The Renin-Angiotensin-Aldosterone System

Blockers of the renin-angiotensin-aldosterone system

Controlling and Regulating the blood pressure. The kidney and the central nervous system are the critical components. The role of peripheral baroreceptors and the autonomic nervous system is important.

**Medical therapy for MI patients: ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs)**

ACE inhibitors and ARBs decrease blood pressure and decrease the work of the heart by dilating arteries. Side effects are cough, dizziness and low blood pressure. A contraindication is a pregnancy.

The kidney is crucial to blood pressure regulation—the juxtaglomerular apparatus and renin release. Renin initiates a biochemical sequence that eventually converts angiotensinogen, produced in the liver into angiotensin, a strong vasoconstrictor. Angiotensin stimulates the release of aldosterone from the adrenal gland, which causes the kidney to retain salt (NaCl) and water. Angiotensin stimulates the release of anti-diuretic hormone from the pituitary gland which causes the kidney to retain water.
Decreased kidney function can make the kidney worse. ACE-inhibitors could lower the blood level too much and cause allergic reactions. This system is part of the body’s defense against dehydration and/or blood loss. The idea is to restore blood volume to normal as quickly as possible.

<table>
<thead>
<tr>
<th>Commonly used ACEI and All blockers</th>
<th>Initial daily dose(s)</th>
<th>Target dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Captopril</strong></td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td><strong>Enalapril</strong></td>
<td>2.5 mg bid</td>
<td>10—20 mg bid</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>5—10 mg daily</td>
<td>40 mg daily</td>
</tr>
<tr>
<td><strong>Lisinopril</strong></td>
<td>2.5—5 mg daily</td>
<td>20—40 mg daily</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8—16 mg daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>5 mg bid</td>
<td>20 mg bid</td>
</tr>
<tr>
<td><strong>Ramipril</strong></td>
<td>1.25—2.5 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1 mg daily</td>
<td>4 mg daily</td>
</tr>
<tr>
<td><strong>Candesartan</strong></td>
<td>4—8 mg daily</td>
<td>32 mg daily</td>
</tr>
<tr>
<td><strong>Losartan</strong></td>
<td>25—50 mg daily</td>
<td>50—100 mg daily</td>
</tr>
<tr>
<td><strong>Valsartan</strong></td>
<td>20—40 mg bid</td>
<td>160 mg bid</td>
</tr>
</tbody>
</table>

AE’s with ACEI and ARB — first-line Rx

1. Alpha blockers work on the blood muscles to open up the blood vessels while the Beta medications work on the heart to ease the flow of blood.
2. Alpha meds work on the hormone of norepinephrine or noradrenaline while the Beta works on the epinephrine or adrenaline.
3. Alpha blockers work for the blood pressure levels alone while the Beta blockers can work for both heart and the blood pressure.

4. Beta blockers can cause weight gain while Alpha medications do not.

Review Questions on Alpha and Beta Blockers

The correct answers can be found below the references.

1. Which of the following alpha blocker was once used for the treatment of erectile dysfunction?
   - A. Prazosin
   - B. Doxazosin
   - C. Yohimbine
   - D. Propranolol
   - E. Nadolol

2. Which of the following drug causes orthostatic hypotension as a side effect?
   - A. Prazosin
   - B. Propranolol
   - C. Nadolol
   - D. Atenolol
   - E. Metoprolol

3. Which of the following beta-blocker is not a cardioselective in its action?
   - A. Propranolol
   - B. Atenolol
   - C. Bisoprolol
   - D. Esmolol
   - E. Acebutolol

References


Reid, J. L. (1986). Alpha-adrenergic receptors and blood pressure control. The American Journal of Cardiology, 57(9), 6E-12E.

Correct answers: 1C, 2A, 3A

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