

β - Adrenoceptors blockers

Prof. Hanan Hagar
Pharmacology Unit
College of Medicine

Classification of β -Adrenoceptors Blockers

Selective β_1 antagonists

Atenolol, Bisoprolol

Esmolol, Metoprolol

(CAT BITES ME)

Non selective β - Antagonists

Blocks β_1 & β_2 receptors

Propranolol

Sotalol, Timolol (PST)

Mixed α , β receptors blockers

➤ **Carvedilol**

➤ **Labetalol**

β ADRENOCEPTOR BLOCKERS

Pharmacodynamic Classification

1

According to selectivity

Non-Selective

Block β_1 & β_2

Propranolol, Sotalol, Timolol (Eye)

Labetalol, Carvedilol (mixed α , β blockers)

Selective

Block β_1

Atenolol, Bisoprolol, Metoprolol, Esmolol

2

According to presence of agonistic/antagonistic action;
Intrinsic Sympathomimetic Activity (ISA)

Without ISA

Atenolol, Bisoprolol, Metoprolol

Propranolol, Sotalol, Timolol, carvedilol

With ISA (may activate beta receptors)

labetalol

3

According to presence of membrane stabilizing effects i.e. **Block Na Channels**
Quinidine-like action
Antiarrhythmic action

Propranolol, labetalol

β ADRENOCEPTOR BLOCKERS

Pharmacokinetic Classification

According to their lipid solubility

Lipophilic

Hydrophilic

	Lipophilic	Hydrophilic
Oral absorption	Complete	Irregular
Liver metabolism	Yes	No
$t_{1/2}$	Short	Long
CNS side effects	High	low
	Metoprolol Propranolol, Timolol Labetalol , Carvedilol	Atenolol, Bisprolol, Esmolol Sotalol

CNS depressant effects i.e. **Sedative effect** → ↓ **Anxiety**

Pharmacokinetics of β -blockers:

- Most of them are lipid soluble
- **Lipid soluble β -blockers**
 - well absorbed orally.
 - are rapidly distributed, cross readily BBB
 - Have CNS depressant actions
 - Metoprolol, propranolol, timolol, labetalol, carvedilol
- Most of them have half-life from 3-10 hrs except **Esmolol (10 min. given intravenously)**.
- Most of them metabolized in liver & excreted in urine.

β -Adrenergic receptors :

β_1 (Heart):

- **Increase heart Rate → Positive chronotropic effect.**
- **Increase in contractility → Positive inotropic action.**
- **Increase in conduction velocity → Positive dromotropic.**

β_2 : relaxation of smooth muscles

β_2 : Hyperglycemia

β_2 : ↑ Release of glucagon from pancreas

β_2 α_1 : Glycogenolysis & gluconeogenesis in liver

β_3 : ↑ Lipolysis by adipose tissue

Pharmacological actions of β -Adrenergic blockers:

CVS:

- **Negative inotropic, chronotropic, dromotropic \rightarrow \downarrow CO**

Antianginal effects (ischemic heart disease):

- **\downarrow Heart rate (bradycardia)**
- **\downarrow force of contraction \rightarrow \downarrow cardiac work**
- **\downarrow Oxygen consumption due to bradycardia**

Anti-arrhythmic effects:

- **\downarrow excitability, \downarrow automaticity & \downarrow conductivity (due to its sympathetic blocking).**

Pharmacological actions of β -Adrenergic blockers:

Blood vessels β_2

↑ peripheral resistance (PR) by blocking vasodilatory effect β_2

↓ blood flow to organs → cold extremities

contraindicated in peripheral diseases like **Reynaud's disease**

Blood pressure

Antihypertensive → ↓ BP in hypertensive patients due to effects on:

✚ Inhibiting heart properties → ↓ **cardiac output (β_1)**

✚ β Blockade ↓ renin secretion ↓ Ang II & aldosterone secretion (β_1).

✚ Presynaptic inhibition of NE release from adrenergic nerves

Pharmacological actions of β -Adrenergic blockers:

Respiratory tract: β_2

- Bronchoconstriction
- **contraindicated** in asthmatic patients.

Eye:

↓ aqueous humor production from ciliary body

↓ Reduce intraocular pressure (IOP)

e.g. timolol as eye drops

Intestine:

↑ Intestinal motility

Pharmacological actions of β -Adrenergic blockers:

Metabolic effects:

- Hypoglycemia

- \downarrow glycogenolysis in liver
- \downarrow glucagon secretion in pancreas
- \downarrow lipolysis in adipocytes
- Na^+ retention 2ndry to \downarrow BP \rightarrow \downarrow renal perfusion
- All β -Adrenergic blockers mask hypoglycemic manifestations in diabetic patients \rightarrow **COMA**

Clinical Uses of β -receptor blockers

- **Cardiovascular disorders**
 - **Hypertension**
 - **Arrhythmia**
 - **Angina pectoris**
 - **Myocardial infarction**
 - **Congestive heart failure**
- **Pheochromocytoma**
- **Chronic glaucoma**
- **Hyperthyroidism (thyrotoxicosis)**
- **Migraine prophylaxis**
- **Anxiety**

Clinical Uses of β -receptor blockers

In Hypertension:

Propranolol, atenolol, bisoprolol

Labetalol: α , β blockers

in hypertensive pregnant & hypertensive crisis.

In cardiac arrhythmias:

In supraventricular & ventricular arrhythmias.

Bisoprolol and carvedilol are preferred

Angina pectoris:

- \downarrow heart rate, \downarrow cardiac work & oxygen demand.
- \downarrow the frequency of angina episodes.

Clinical Uses of β -receptor blockers

Congestive heart failure:

e.g. carvedilol:

- **antioxidant** and non selective α, β blocker
- \downarrow myocardial remodeling & \downarrow risk of sudden death.

Myocardial infarction:

Have cardio-protective effect

- \downarrow infarct size
- \downarrow morbidity & mortality \rightarrow
- \downarrow myocardial O₂ demand.
- Anti-arrhythmic action.
- \downarrow incidence of sudden death.

In glaucoma

e.g. Timolol as eye drops

In Hyperthyroidism

- **Protect the heart against sympathetic over stimulation**
- **Controls symptoms; tachycardia, tremors, sweating.**

In anxiety (Social and performance type)

e.g. Propranolol

Controls symptoms; tachycardia, tremors, sweating.

Migraine:

Prophylactic

↓ reduce episodes of chronic migraine

↓ catecholamine-induced vasodilatation in the brain vasculature

e.g. propranolol

Pheochromocytoma

used with α -blockers (**never alone**)

- α -blockers lower the elevated blood pressure.
- β -blockers protect the heart from NE.

Adverse Effects of β -Adrenoceptors blockers

Due to blockade of β_1 - receptor:

- **Bradycardia, hypotension, heart failure**

Due to blockade of β_2 - receptor:

only with non-selective β blockers

- **Hypoglycemia**
- **Bronchoconstriction (# Asthma, emphysema).**
- **Cold extremities & intermittent claudication → by vasoconstriction**
- **Erectile dysfunction & impotence**
- **↑ TG hypertriglycerides**
- **Coronary spasm → in variant angina patients**
- **All β -Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating,... → COMA**

Adverse Effects of β -Adrenoceptors blockers

- ✚ Depression, and hallucinations.
- ✚ Gastrointestinal disturbances.
- ✚ Sodium retention

Precautions

Sudden stoppage will give rise to a withdrawal syndrome:

Rebound angina, arrhythmia, myocardial infarction &

Hypertension **WHY ? → Up-regulation of β -receptors.**

To prevent withdrawal manifestations → drug withdrawn gradually.

Contraindications of β -Adrenoceptors blockers

- **Heart Block** (beta blockers can precipitate heart block).
- **Bronchial Asthma** (safer with cardio-selective β -blockers).
- **Peripheral vascular disease** (safer with cardio-selective β -blockers).
- **Diabetic patients** → Masking of hypoglycaemia / **GIVEN CAUSIOUSLY**
- **Hypotension**
- **Alone in pheochromocytoma** (must be given with an α -blockers).

PROPRANOLOL

Is the chosen as prototype

Non-Selective Competitive Blocker of β_1 & β_2

Membrane stabilizing action/ quinidine-like /local anesthetic effect
sedative actions /No ISA

Kinetics

Lipophilic, completely absorbed, 70% destroyed during 1st pass hepatic metabolism, 90-95% protein bound, cross BBB and excreted in urine.

Can be given p.o or parenteral

Dynamics

β -blocking Effect:

Membrane Stabilization: Block Na channels → direct depressant to myocardium → has local anesthetic effect (**anti-arrhythmic effects**).

CNS Effect: Has **sedative action** ↓ tremors & anxiety → used to protect against social anxiety performance anxiety.

PROPRANOLOL

Actions

Heart: by **block β_1**

Inhibit heart properties → ↓ cardiac output

Has anti-ischemic action → ↓ cardiac work + ↓ O₂ consumption

Has anti-arrhythmic effects → ↓ excitability, automaticity & conductivity
+ by membrane stabilizing activity

BP: by **block β_1 & β_2**

Has antihypertensive action by →

✚ Inhibiting heart properties → ↓ cardiac output

✚ B blockade : ↓ renin & RASS system

✚ Presynaptic inhibition of NE release from adrenergic nerves

✚ Inhibiting sympathetic outflow in CNS

PROPRANOLOL

Actions

Cont.

Blood Vessels [BV]: by **block β_2**

Vasoconstriction → ↓ **blood flow specially to muscles, other organs except brain** cold extremities

Bronchi: by **block β_2**

Bronchospasm specially in susceptible patients

Intestine: by **block β_2**

↑ Intestinal motility

Metabolism: by **block mainly β_2**

In liver; ↓ **Glycogenolysis** → **Hypoglycaemia**

In pancreas; ↓ **Glucagon secretion**

In adipocytes; ↓ **Lipolysis**

In skeletal muscles; ↓ **glycolysis**

On peripheral & central nervous systems:

Has local anesthetic effect

↓ **tremors** & ↓ **anxiety**

PROPRANOLOL

INDICATIONS

- + Hypertension
- + Arrhythmias
- + Angina
- + Myocardial infarction
- + Migraine [*Prophylaxis*]
- + Pheochromocytoma; used with α -blockers (never alone)
- + Chronic glaucoma
- + Tremors
- + Anxiety; (*especially social & performance type*)
- + Hyperthyroidism

LABETALOL

Blocks α_1 & β

Rapid acting, non-selective with ISA & local anesthetic effect

Do not alter serum lipids or blood glucose

Used in → given p.o and i.v;

Severe hypertension in pheochromocytoma

Hypertensive crisis (e.g. during abrupt withdrawal of clonidine).

Used in pregnancy-induced hypertension

ADR: Orthostatic hypotension, sedation & dizziness

CARVEDILOL

Blocks α_1 & β

Non-selective with **no ISA & no local anesthetic effect.**

Has **ANTIOXIDANT** action

Favorable metabolic profile.

Used effective in → **CONGESTIVE HEART FAILURE** → reverses its pathophysiological changes.

ADR: Edema

Selective β_1 -receptor blockers

- **Selectivity present in low doses but is lost at high doses**
- **no change in lipid or glucose**
- **no bronchoconstriction**
- **are preferable in patients**
 - **With asthma, COPD**
 - **Raynaud's phenomenon & PVD**
 - **Diabetics/ Dyslipidemias.**
 - **Variant Angina (coronary spasm).**

Summary of B-blockers uses

- **Hypertension** Atenolol, Bisoprolol > Metoprolol, Propranolol
- **cardiac arrhythmia** Esmolol (ultra-short acting), Atenolol, Propranolol
- **Congestive heart failure** Carvedilol, Bisoprolol, Metoprolol
- **Myocardial infarction** Atenolol, Metoprolol, Propranolol
- **Glaucoma** Timolol
- **Migraine prophylaxis** Propranolol
- **Relief of anxiety (social & performance)** Propranolol
- **Thyrotoxicosis** Propranolol

β -receptor blockers

Propranolol	Non selective B_1, β_2 blocker	Migraine prophylaxis Hyperthyroidism (thyrotoxicosis) Relieve anxiety (social performance)
Timolol	B_1, β_2 blocker	Glaucoma
Atenolol Bisoprolol Metoprolol	B_1 blocker	Myocardial infarction Hypertension
Esmolol	B_1 blocker Ultra short acting	Cardiac arrhythmia
Carvedilol	Non selective α, B blocker	Congestive heart failure
Labetalol	α, B blocker	Hypertension in pregnancy Hypertensive emergency