

# **β-ADRENERGIC BLOCKING DRUGS**

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## Introduction

- The ANS has two divisions-sympathetic and parasympathetic.
- The sympathetic division arises from thoracolumbar region ( $T_1$ - $L_3$ , thoracolumbar outflow).
- The parasympathetic division arises from two separate regions in the CNS,
- The cranial outflow arises from cranial nerves (III, VII, IX and X) and sacral outflow from  $S_2$ ,  $S_3$  and  $S_4$  spinal roots.

## Contd..

- Most of the visceral organs have dual nerve supply, i.e. they are supplied by both divisions of the ANS, but effects of one system predominate.
- The ciliary muscle, pancreatic and gastric glands receive only parasympathetic supply.
- Sweat glands, hair follicles, spleen and most of the blood vessels have only sympathetic supply.

## Types of adrenergic receptors

- Adrenergic receptors are divided into  $\alpha$  and  $\beta$  types, which are located on the cell membrane.
- All adrenergic receptors are G-protein coupled receptors and regulate the production of intracellular second messengers; increase in IP3/DAG ( $\alpha_1$ ),  $\downarrow$ cAMP ( $\alpha_2$ ) and  $\uparrow$ cAMP ( $\beta$ ).
- $\alpha$  receptor is further divided into  $\alpha_1$  &  $\alpha_2$ , and  $\beta$  receptor into  $\beta_1$ ,  $\beta_2$  &  $\beta_3$ .

# Classification of $\beta$ -Adrenergic Blockers

## ❖ First generation (Older, nonselective):

- Propranolol
- Timolol
- Sotalol
- Pindolol

## ❖ Second generation ( $\beta_1$ or Cardioselective):

- Metoprolol
- Atenolol
- Acebutolol
- Bisoprolol
- Esmolol

❖ Third generation (With  $\alpha$  blocking and/or vasodilator property):

- Labetalol
- Carvedilol
- Celiprolol
- Nebivolol
- Betaxolol

❖  $\beta$ -Blockers with intrinsic sympathomimetic activity  
(Partial agonists at  $\beta_1$  receptor):

- Celiprolol
- Pindolol
- Alprenolol
- Acebutolol

❖  $\beta$ -Blockers having membrane stabilizing property/ $\text{Na}^+$  channel blockers/local anaesthetic property:

- Propranolol (max.)
- Metoprolol
- Labetalol
- Acebutolol
- Pindolol

❖  $\beta$ -Blockers having water solubility(C/I in Renal failure):

- Atenolol
- Nadolol (longest acting)
- Sotalol

## Pharmacokinetics

- Propranolol is the prototype drug.
- It is highly lipid soluble and is well absorbed from GI tract.
- The bioavailability of propranolol is low because of its extensive first-pass metabolism.
- It is highly bound to plasma proteins; has large volume of distribution; freely crosses BBB, and metabolites are excreted in urine.

## Contd..

- Average dose:- 40-160mg/day.
- Start with a low dose and gradually increase according to need; i.v.-2 to 5 mg injected over 10 min with constant monitoring.
- It is not injected s.c. or i.m. because of irritant property.

# Esmolol

- It is administered intravenously; 0.5mg/kg.
- It is rapidly metabolized by esterases in RBC;  $t_{1/2}$  is about 10 min.
- It is a selective  $\beta_1$ -blocker and has a short duration of action.
- It is used for rapid control of ventricular rate in supraventricular arrhythmias.

# Carvedilol

- It blocks  $\beta_1$ ,  $\beta_2$ , and  $\alpha_1$ -adrenergic receptors.
- It has antioxidant, antiproliferative, and vasodilatory properties.
- It has cardioprotective effect; hence, long term use reduces mortality in patients with CHF.
- Dose for CHF: start with 3.125 mg BD for 2 weeks, if well tolerated, gradually increase to max. of 25mg BD.
- For hypertension/angina: 6.25 mg BD to 25mg BD.

## Adverse Effects of $\beta$ -Blockers

### 1) CVS:

- Bradycardia, heart block and may precipitate CHF in patients with low cardiac reserve.
- It may worsen peripheral vascular disease.
- It can exacerbate Prinzmetal angina (variant angina) due to unopposed  $\alpha_1$ -action, hence are C/I in this condition.

## 2) Respiratory system:

- Blockade of  $\beta_2$ -receptors in the bronchial smooth muscle can cause severe bronchospasm in patients with asthma and COPD. Hence, are C/I.

## 3) CNS:

- Sleep disturbances, hallucinations, fatigue and mental depression.

#### 4) Metabolic:

- Recovery from hypoglycaemia (induced by antidiabetic drugs) is delayed by  $\beta$ -blockers.
- It may mask the warning signs and symptoms of hypoglycaemia.

#### 5) Withdrawal symptoms:

- Abrupt withdrawal of  $\beta$ -blockers after chronic use is dangerous because angina or frank myocardial infarction and even sudden death can occur(due to upregulation of  $\beta$ -receptors).

## Drug Interactions

### I) Propranolol X verapamil:

- They produce additive cardiac depressant effects and may cause CCF, bradyarrhythmias, heart block or even cardiac arrest.

### II) Cholestyramine and colestipol X $\beta$ -blockers:

- Cholestyramine and colestipol are bile acid-binding resins.
- They bind to  $\beta$ -blockers in the gut and interfere with the absorption of  $\beta$ -blockers.

### III) Propranolol X lignocaine:

- Propranolol reduces the clearance of lignocaine by decreasing hepatic blood flow.

### IV) Propranolol X NSAIDs:

- NSAIDs by inhibiting PG synthesis promote Na<sup>+</sup> and water retention on chronic use.
- Thus, they decrease antihypertensive effect of  $\beta$ -Blockers.

### V) Propranolol X Chlorpromazine: Propranolol interferes with the first-pass metabolism of chlorpromazine and increases its bioavailability.

# Therapeutic Uses of $\beta$ -Blockers

## □ Cardiac indications:

- Hypertension
- Angina (classical)
- MI
- Chronic CHF
- Arrhythmia
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Dissecting aortic aneurysm

## ❑ Extra cardiac indications:

- Thyrotoxicosis
- Glaucoma
- Akathisia (DOC)
- Migraine
- Essential tremors
- Performance anxiety
- Pheochromocytoma
- Alcohol withdrawal

*Thank you*