

Preclinical Screening Methods of Cardiovascular Pharmacology

Antihypertensives – Preclinical Screening Methods

- **Antihypertensive drugs are used to lower high blood pressure (hypertension). Hypertension occurs due to:**
 - Increased peripheral resistance (vasoconstriction)
 - Increased cardiac output
 - Overactivity of renin-angiotensin system
- **These drugs act by:**
 - Dilating blood vessels (vasodilators)
 - Reducing heart activity (β -blockers)
 - Inhibiting ACE (angiotensin converting enzyme)
 - Increasing salt and water excretion (diuretics)

Objectives of Screening

- To evaluate blood pressure lowering effect
- To study mechanism (ACE inhibition, β -blockade, etc.)
- To assess long-term cardiovascular protection
- To detect side effects (hypotension, reflex tachycardia)

In Vivo Methods (Animal Models)

A. Spontaneously Hypertensive Rats (SHR)

- **Principle:** These rats naturally develop high blood pressure
- **Method:**
 - Administer test drug chronically
 - Measure systolic and diastolic blood pressure
- **Observation:** Reduction in blood pressure = antihypertensive effect
- **Importance:** Closely mimics human essential hypertension

B. DOCA-Salt Induced Hypertension Model

- **Principle:** Deoxycorticosterone acetate (DOCA) + salt causes hypertension
- **Method:** Administer DOCA and high salt diet
- **Observation:** Reduction in BP after drug = effective agent

C. Renal Artery Ligation Model

- **Principle:** Reduced kidney blood flow activates renin-angiotensin system
- **Method:** Partially constrict renal artery
- **Observation:** Drug reduces BP by blocking RAAS system

D. Blood Pressure Measurement Techniques

- **Non-invasive:** Tail-cuff method in rats
- **Invasive:** Direct arterial cannulation
- **Parameters:**
 - Systolic BP
 - Diastolic BP
 - Mean arterial pressure

In Vitro Methods

1. ACE Inhibition Assay

- Measures ability to inhibit angiotensin conversion
- Important for ACE inhibitors

2. Isolated Aortic Ring Assay

- **Method:** Aorta mounted in organ bath
- **Observation:** Relaxation = vasodilator activity

3. Receptor Binding Studies

- **Evaluation:**
 - α 1 receptors
 - β 1 receptors
 - Angiotensin receptors

Other Alternative Models

- **Cell cultures:** Vascular smooth muscle cells
- **Zebrafish:** Used for cardiovascular studies

Parameters Measured

- Blood pressure levels
- Heart rate
- Vascular resistance

- Hormonal levels (renin, angiotensin)

Toxicological Considerations

- Excessive hypotension
- Electrolyte imbalance
- Kidney dysfunction

Antiarrhythmic Agents – Preclinical Screening Methods

- **Arrhythmias are abnormal heart rhythms caused by:**
 - Disturbed electrical conduction
 - Abnormal ion channel function
- **Antiarrhythmic drugs act by:**
 - Blocking sodium (Na^+) channels
 - Blocking potassium (K^+) channels
 - Blocking calcium (Ca^{2+}) channels
 - Modulating autonomic activity

Objectives of Screening

- To evaluate antiarrhythmic activity
- To study electrophysiological effects
- To assess safety (proarrhythmic risk)
- To identify ion channel effects

In Vivo Methods (Animal Models)

A. Aconitine-Induced Arrhythmia

- **Principle:** Aconitine increases sodium channel activity → arrhythmia
- **Method:** Administer aconitine
- **Observation:** Prevention of arrhythmia = antiarrhythmic effect

B. Calcium Chloride-Induced Arrhythmia

- **Principle:** High Ca^{2+} causes abnormal cardiac contractions
- **Observation:** Reduction in arrhythmia = calcium channel blocking effect

C. Adrenaline-Induced Arrhythmia

- **Principle:** Excess adrenergic stimulation causes arrhythmia
- **Observation:** Reduction = β -blocking activity

D. Ischemia-Reperfusion Model

- **Principle:** Reduced blood flow followed by restoration causes arrhythmia
- **Observation:** Decreased arrhythmia incidence = protective effect

E. ECG Monitoring

- **Parameters:**
 - Heart rate
 - PR interval
 - QRS complex
 - QT interval
- **Observation:** Normalization of ECG = antiarrhythmic effect

In Vitro Methods

1. Ion Channel Studies

- **Measure effects on:**
 - Sodium channels
 - Potassium channels
 - Calcium channels

2. Isolated Heart Preparation (Langendorff)

- Heart is perfused outside body
- **Measures:**
 - Heart rate
 - Contractility
 - Electrical activity

3. Patch Clamp Technique

- Measures ion channel currents at cellular level

Other Alternative Models

- **Cell cultures:** Cardiomyocytes
- **Zebrafish:** Used for cardiac rhythm studies

Parameters Measured

- Heart rhythm
- ECG changes
- Arrhythmia duration
- Survival rate

Toxicological Considerations

- Proarrhythmic effects (can worsen arrhythmia)
- Cardiac depression
- Hypotension

Antianginal Agents – Preclinical Screening Methods

- Angina pectoris is chest pain caused by reduced blood supply (ischemia) to the heart muscle.
- **This happens when:**
 - Oxygen demand of heart increases
 - Oxygen supply decreases due to narrowed coronary arteries
- **Antianginal drugs act by:**
 - Reducing oxygen demand (β -blockers)
 - Increasing oxygen supply (vasodilators like nitrates)
 - Improving coronary blood flow (calcium channel blockers)

Objectives of Screening

- To evaluate anti-ischemic activity
- To assess improvement in coronary blood flow
- To study effect on heart workload
- To identify mechanism of action

In Vivo Methods (Animal Models)

A. Coronary Artery Ligation Model

- **Principle:** Blocking coronary artery causes myocardial ischemia
- **Method:** Ligate coronary artery in animals (rats/dogs)
- **Observation:**
 - Reduced infarct size = antianginal effect



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