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**CALCIUM
CHANNEL
BLOCKERS (CCBS)**

CALCIUM CHANNELS

◎ **4 types :-**

◎ **1) Voltage sensitive Ca^{2+} channels :- 5 subtypes :-**

◎ **2) Receptor – operated Ca^{2+} channels**

◎ **3) Leak channels or Stretch- operated channels**

◎ **4) Na^{+} - Ca^{2+} Exchange Channel**

VOLTAGE SENSITIVE Calcium Channels

- ◎ **5 subtypes :- ** L,T,N,P & Q.**
- ◎ **** L-Type Ca²⁺ - channels - dominant in Cardiac muscles, Smooth Muscles, SA & AV nodes - blocked by CCBs.**
- ◎ **** T,N,P,Q are present in thalamic, cerebellar - less affected by CCBs.**
- ◎ **Voltage-gated Ca²⁺ contains :-
Activated Gate (AG) - extracellularly
Inactivated Gate (IG) - intracellularly
Stereo-selective Drug Receptor sites
for CCBs**

VOLTAGE SENSITIVE L-Type Calcium Channels

- ⦿ **Binding of CCBs :-**
- ⦿ **→ Reduces the frequency of opening of voltage gated Ca²⁺ channels**
- ⦿ **→ Decreases trans-membrane Ca²⁺ current → Smooth muscle relaxation**
- ⦿ **→ Reduction in cardiac contractility**
- ⦿ **→ Decrease in pacemaker activity in SA node**
- ⦿ **→ Decrease in conductivity in AV node.**

RECEPTOR - OPERATED Calcium Channels

- ⦿ **NE, AT II → increases Ca²⁺ entry through these channels**
- ⦿ **→ Also releases Ca²⁺ from Sarcoplasmic Reticulum**
- ⦿ **→ CCBs poorly blocks these channels**
- ⦿ **→ Block produced by CCBs can be reversed by α-1 agonists → ↑ Ca²⁺ + influx through DAG-IP3 pathway.**

LEAK OR STRETCH OPERATED CHANNELS

- **Present in blood vessels**
- **Increase Ca^{2+} - influx on being stretched**
- **Small amount of Ca^{2+} keep on Leaking into resting cell and are pumped out by Ca^{2+} ATPase**
- **Mechanical stretch → activates Leak/Stretch channels → promotes inward movement of Ca^{2+} .**

Na⁺-Ca²⁺ Exchange Channel

- **Present in Heart , Blood vessels**
- **Involved in the action of Digitalis**
- **CCBs do not block Na⁺-Ca²⁺ exchange channel.**

CALCIUM CHANNELS BLOCKERS (CCBs)

- **I) Phenylalkylamines :-**
Verapamil ($t_{1/2}$ – 6 hrs)
- **II) Benzothiazepines :-**
Diltiazem ($t_{1/2}$ – 4 hrs)
- **III) Dihydropyridines :-**
 - **(a) Short Acting :** Nifedipine
($t_{1/2}$ - 2-6 hrs)
 - **(b) Intermediate Acting :-**
Nitrendipine ($t_{1/2}$ – 8-12hrs)
 - **© Long Acting :** Amlodipine
($t_{1/2}$ – 30- 50 hrs)

CALCIUM CHANNEL BLOCKERS (CCBs) - Actions

① **1) Vascular Smooth Muscles (VSM) :-**

① → ↓ iCa^{2+} → Relaxes VSM

① → Relaxes Arterioles →

↓ peripheral resistance →

↓ Afterload → ↓ BP.

NO EFFECT ON PRELOAD(on veins)

2) Extravascular SM (EVSMs) :-

→ **Inhibit PDEs & ↑ cAMP levels**

→ **Relaxes EVSMs**

CCBs - Actions (Contd..)

- ③ **3) Heart :- ↓ Ca²⁺ entry →**
- ③ ↓ HR (Negative Chronotropic Effect)
- ③ ↓ Automaticity & Conductivity by slowing rate of recovery
- ③ (Therefore, **VERAPAMIL** is used in treatment of **PSVT** – Paroxysmal Supra-ventricular Tachycardia).

- ③ **VERAPAMIL** → Cardioselective
- ③ **NIFEDIPINE** → SM selective
- ③ **DILTIAZEM** → Intermediate

CCBs - Actions (Contd..)

- ⊙ **4) Haemodynamic Effect :-**
- ⊙ **↑ Coronary artery dilatation**
- ⊙ **↓ Coronary Vascular Resistance**
- ⊙ **Produces Epicardial and Intra-myocardial arteries dilatation**
- ⊙ **↑ Coronary Blood Flow through both Epicardial , Intramyocardial arteries → prevents coronary vasospasm → Useful in Vasospastic angina.**
- ⊙ **Produces vasodilatation in Pulmonary & Peripheral vessels**

CCBs - Comparison

Proper	Vera	Diltia	Nife
HR	↓	↓	↑
AV Block	Severe	Moderate	No BK
My Contr	↓ Mod	↓ Mild	No Eff
Antiarrhy	Mild	Nil	Nil
VSM Dilat	Mod	Mild	Severe
Reflex Sym	Mild	Mod	No
- Acti Block	Blk	Blk	Blk
Bioavail	20-35%	40%	60%
T1/2-hrs	6-12	3-5	5, 35 Aml
S/Es	AV Blk, Const, LVF	AV Blk ↓BP, LVF	Palpita ↓BP, Edema
Uses	Angina, ↑BP, PSVT	Angina ↑BP	Angina HF

Amlodipine - Advantages

- ⦿ **Long acting CCB.**
- ⦿ **Slow onset, but prolong duration of action**
- ⦿ **Less reflex sympathetic stimulation → Lesser tachycardia → lesser tendency to increase cardiac work.**
- ⦿ **Unlike SA – CCBs → amlodipine do not produce post-MI mortality → Hence, favoured currently.**

Amlodipine - Advantages

- ⦿ **Longer half-life (30-50 hrs).**
- ⦿ **Given once daily**
- ⦿ **Lesser first-pass metabolism**
- ⦿ **Consistent bioavailability**
- ⦿ **Slow but complete oral absorption**
- ⦿ **Avoids day time fluctuations in bloods levels**
- ⦿ **Therefore, avoids early side effects related to vasodilatation → flushing, hypotension, reflex tachycardia and headache**

CCBs -- Advantages

- ① **Prominent relaxant effect on large arteries – More beneficial in Elderly patients.**
- ② Improve arterial compliance, **retard atherogenesis and regress left ventricular heart failure.**
- ③ Do not increase airway resistance – **Can be used in asthmatics.**
- ④ Safely **used in Variant angina, PVD pts.**

CCBs – Advantages

- ⦿ Do not compromise **hemodynamic functions**
- ⦿ Maintain adequate cerebral perfusion – **No sedation or CNS effects**
- ⦿ **Do not impair renal perfusion**
- ⦿ Do not impair male sexual activity or **physical work capacity.**
- ⦿ No deleterious **effect on lipid profile, uric acid levels or glucose metabolism**

CCBs - Advantages

- ⦿ **Postural hypotension, first – dose phenomenon or rebound phenomenon not observed.**
- ⦿ Produces **natri-uretic effect** – **Hence, diuretics are not combined.**
- ⦿ Can be **prescribed during pregnancy** -- No adverse effects on foetus. **(But to be stopped during labour)**
- ⦿ Do not hamper **QOL.**

CCBs - USES

- ① **1) Hypertension**
- ② **2) Angina (vasospastic)**
- ③ **3) Myocardial Infarction (MI)**
- ④ **4) PSVT (Verapamil – IV)**
- ⑤ **5) Nifedipine – was also used in → Hypertensive Emergencies,**
- ⑥ **6) Migraine Prophylaxis,**
- ⑦ **7) Stroke, Premature labor**
- ⑧ **8) Peripheral Vascular Disorders**

CCBs – Adverse Effects

- ⦿ **Dizziness, Fatigue, Orthostatic Hypotension,**
- ⦿ **Palpitation (Nifedipine)**
- ⦿ **Leg cramps, Ankle edema**
- ⦿ **Constipation, Gingival Hyperplasia, Difficulty in voiding urine.**
- ⦿ **HF (Verapamil, Diltiazem), Hampering of Diabetes control.**

CCBs - Contraindications

- ⦿ **HF, cardiogenic shock**
- ⦿ **First,second degree AV block**
- ⦿ **Atrial Fibrillation**
- ⦿ **Wolff- Parkinson – Syndrome**
- ⦿ **Ventricular Tachycardia**
- ⦿ **Hypotension**
- ⦿ **Prostatic Hypertrophy**

CCBs - Precautions

- **Verapamil :-**
- IV use produces cardiac arrest in pts with sick sinus syndrome
- Not to be given with Beta-Blockers, Digitalis (increases digitalis toxicities)
- Not to be given with Quinidine, Disopyramide