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HALLMARKS OF CALCIUM CHANNEL BLOCKERS: A REVIEW

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ABSTRACT

Calcium channel blockers (CCBs) were unveiled during screening of coronary artery dilators. They work as inhibitors of calcium ions influx through ion specific channels leading to smooth muscle relaxation and ultimately vasodilation. This inhibitory effect also accounts for contractility reduction in the myocardium. They are predominantly discriminated into two classes named as Dihydropyridines (DHPs) and Non-dihydropyridines (NDHPs). DHPs selectively work in vasculature and clinically useful as antihypertensives. They have also found application in stable and vasospastic angina. While NDHPs are more negatively ionotropic and chronotropic and this feature makes them useful in arrythmias management. As 2nd or 3rd line agents, calcium channel blockers are suggested to hypertensive diabetic patients. Nifedipine (a dihydropyridine calcium channel blocker) is now recommended safe for post-operative hypertension management in children of all age groups. Anginal patients unresponsive to β-blocker therapy or contraindicated to it, are successfully managed by calcium channel blockers. CCBs have also been found effective for the prevention of recurrence of myocardial infarction. Evidences exist supporting their efficacy in Raynaud's phenomena, Glaucoma, and in the management of preterm labor. Besides that, these agents have also been found safer in 1st trimester of pregnancy. Novel additions in calcium channel blockers with tendencies to block channels other than L-type have provided a new insight for future research, as they confer additional properties of cardioprotection, neuroprotection and renoprotection.

KEYWORDS: Calcium Channel Blockers; Dihydropyridines; Non- dihydropyridines; Hypertension.

1. INTRODUCTION

CCBs were discovered during experimentation upon tiny molecules aimed to screen for coronary artery dilatation effect. The contributing mechanism was found to be blockade of calcium influx and so they were named as calcium channel blockers.[1,2] In 1883, Sidney Ringer discovered and reported the role and significance of calcium ions in muscle contraction. Then, in the middle of 1960s, pharmacological studies of calcium function were commenced and therapeutic applications of CCBs were implemented in clinical practice in 1980s.[1] This review is an attempt aimed to comprehensively organize, integrate and investigate the updated information regarding the identification, mechanism of action, pharmacological characteristics of CCBs, their reported clinical uses for cardiovascular pharmacotherapy. Additionally, novelty in the applications of CCBs resulting from discovery of some newer drugs and the recent advancement in clinical outcomes of CCBs achieved through combination therapy is also discussed.

Furthermore, gaps and inconsistencies in the literature published to-date have also been identified in this review and proposed new guidelines for future research.

2. MECHANISM OF ACTION

CCBs work by blocking the extracellular calcium influx through ion selective channels responsible for muscle excitation. Because of this inhibition, relaxation of vascular smooth muscles occurs that leads to vasodilation. While in cardiac muscles, inhibition of calcium flow promotes reduction in myocardial conduction and contractility[3], shown in figure 1.

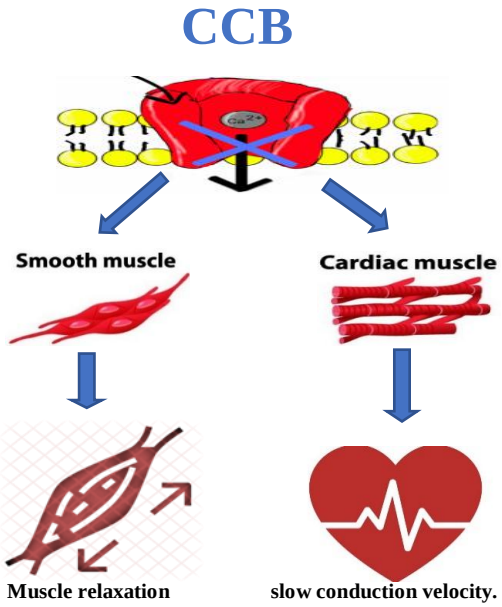

Fig. 1. Schematic illustration of CCBs' Mechanism of Action.

3. CLASSIFICATION

Based on separate binding sites on L-type calcium channels, CCBs are classified into two major classes, shown in table 1.

1-Dihydropyridines (DHPs).

2-Non-Dihydropyridines (NDHPs).

3.1. Dihydropyridines(DHPs)

DHPs are selective for vasculature[2] and exhibit a more potent vasodilatory effect than NDHPs[4], thus beneficial in hypertension (HTN). Furthermore, they are recommended in stable and variant angina of chronic nature as well.[2] Evidences support that long acting DHPs are more protective against complications of HTN than those exhibiting intermediate action.[5]

3.2. Non-Dihydropyridines(NDHPs*)*

NDHPs are known to have greater negative ionotropic and chronotropic effects than DHPs[4] and so they influence myocardialconduction and contraction. This property accounts for their principal use in arrhythmias management or if patients require β-blockers.[6] Their blood pressure lowering tendency is same as DHPs have.[4]

Table 1: Difference between subclasses of CCBs.

	Dihydropyridines	**Non-Dihydropyridines**
Major Site of action	Vasculature	Heart
Pharmacological effect	Vasodilation	Reduction in myocardial conduction and contraction
Clinical use	Hypertension, Angina	Arrythmias

4. CCBS IN CARDIOVASCULAR PHARMACOTHERAPY

4.1. In the Gamut of Antihypertensive Agents

Primary HTN is a complicated clinical condition caused by concurrent abnormal triggering of different compensatory and contra compensatory pathophysiological mechanisms leading to continuous rise in blood pressure levels.

The asymptomatic increase in blood pressure may contribute to occurrence and advancement of target organ damage which enhances the risk of cardiovascular, neurological and renal

morbidity and mortality. Effective hypertension therapy has been shown to prevent damage to blood vessels and to reduce morbidity and mortality.[7] shown in figure 2.

Clinical trials have revealed that DHPs are either equally effective or more effective than other antihypertensive drugs in HTN management and prevention of HTN complications.[8] Therefore, DHPs have been widely recommended for HTN treatment owing to their calcium influx blockade ability into the smooth muscle cells which promotes vasodilation and reduction in total peripheral resistance.[9] Complications of HTN are reduced to greater extent with DHPs than with intermediate acting agents i.e. Diltiazem.[5] Moreover, evidences have been found from previous studies supporting additional benefits of CCBs in patients with compromised cardiovascular system.[2]

Previous studies in the 1990s implied fears regarding the safety of earlier drugs from DHPs group owing to their rapid onset of action and short elimination half-lives which accounts for reflex adrenergic stimulation. However, development of newer drugs[10] e.g. Lercanidipine[11] with characteristics of higher lipophilicity and prolonged duration diminished those safety concerns.[10]

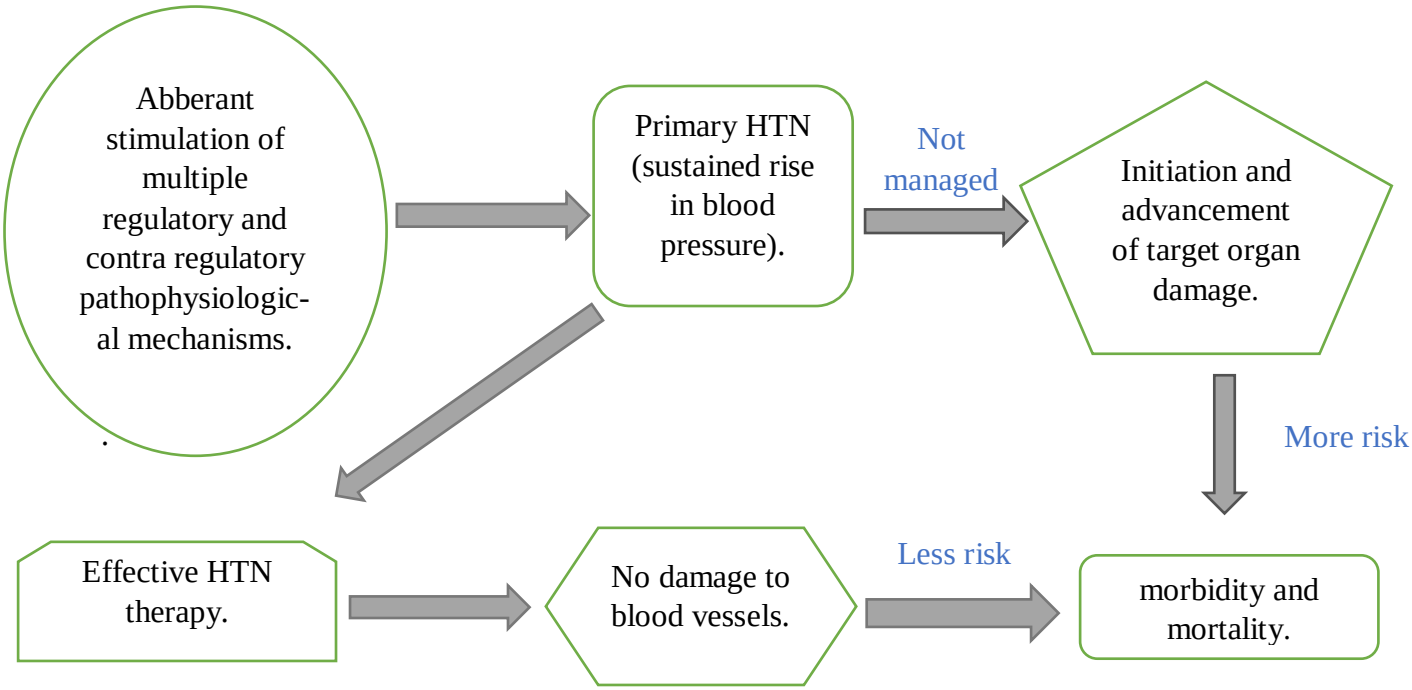

Fig 2: Differential consequences of unmanaged and effectively managed HTN.

4.1.1. As antihypertensives in diabetic population.

Epidemiological studies have found a close relationship between HTN and Diabetes. Presence of one increases the chances of having the other. Improvement of glycemic control has beenobserved in hypertensivediabetic patients treated with CCBs, probably because of restoration of insulin release from pancreatic β-cells and the reduction of apoptosis in β-cells.[9] However, it should be kept in mind that CCBs are supposed to be 2nd or 3rd line drugs in this regard because the preferable 1st line agents for initial management of hypertensive diabetic patients are angiotensin converting enzyme inhibitors (ACEIs) owing to the benefit of reduction in albuminuria provided by them.[12,13] Furthermore, a recent study demonstrated the combination of ACE inhibitors, diuretics and CCBs to be more beneficial, effective and protective against mortality in hypertensive patients with type II Diabetes Mellitus.[14]

4.1.2. Management of post-operative HTN.

Following cardiac surgery, management of post-operative HTN is important for infant and child care. Previously, CCBs were avoided in children below 1 year owing to safety and efficacy concerns. However, a recent study has demonstrated tolerability of Nicardipine (a Dihydropyridine CCB) following cardiac operations in children regardless of age or underlyingdisease. This led to the concept that Nicardipine use should be considered in children (all age groups) to deal with post-operative HTN.[15]

4.2. Management of Vasospastic Angina.

Coronary vessel spasm is one of the contributing factors for the development of Angina pectoris, myocardial infarction and sudden death following ventricular fibrillation.[16] Evidences have shown that CCBs are effective in reducing the frequencies and duration of angina[17] with Benedipine has been found to be more effective than Amlodipine and Diltiazem.[16,18,19] However, CCBs are recommended to those angina patients who do not respond to β- blockers or they are contraindicated.[20]

Management of Supraventricular Arrythmias.

Studies suggest NDHP Verapamil Should be preferred in managing supraventricular arrhythmias[2] since it has negative chronotropic effect on heart and reduces conduction velocity in the myocardium.[4]

4.3. Prevention of Myocardial Reinfarction.

Evidence has been reported from Second Danish Infarction Trial (DAVIT-II) that Verapamil, a NDHP provides protection against reinfarction of the heart.[21]

5. Pleiotropic Actions of CCBs.

Current updates have introduced novel CCBs with tendencies to block channels other than L-type. These include N and T- type CCBs. In addition to provide antihypertensive effect by blocking L-type calcium channels, inhibition of these non-L- type channels have been found to provide cardioprotective, renoprotective and vascular endothelial protective effects.[22] A summary of protective effects of CCBs is shown in table 2.

5.1. Cardioprotective Actions of CCBs

Studies have shown the pleiotropic effects of CCBs for the restoration of vascular endothelial function and so inhibition of atherosclerotic process. The underlying mechanisms include enhancement of Nitric Oxide(NO) synthesis and scavenge of O_2 free radicals.[23,24] High hydrophobicity, structural features with H-donating affinity and resonance stabilizing mechanisms contribute to this antioxidant effect via inhibition of free radical chain reaction.[24,25], In addition to this, some other mechanisms have also been reported from previous studies including inhibition of leukocytes (monocytes) coherence to endothelial cells, inhibition of cell propagation in smooth muscle cells, decline in cholesterol aggregation and cholesterol esterification and acceleration of cholesteryl ester hydrolysis. Furthermore, current updates have demonstrated that the stimulation of peroxisome proliferator-activated receptors gamma (PPAR-ϒ) also account in part for the antiatherosclerotic potential of DHPs.[26] Additionally, a recent study has reported that CCBs are safe and effective in the management of atrioventricular block resulting from coronary spasm.[27]

5.2.Renoprotective Actions of CCBs

T-type CCBs such as Efonidipine, Benedipine, and Azelnidipine have been demonstrated as renoprotective agents[28] since T-type Calcium channels are found in renal vasculature and contribute to renal vasoconstriction.[29] L-type CCBs cause vasodilation of afferent arterioles and contribute to increase in intraglomerular pressure while L/T type and L/N type CCBs ameliorate hypertension related to glomerulus via reduction in intraglomerular pressure.[28,30] Moreover, some non-hemodynamic mechanisms also account for the renoprotective effects of L/T type CCBs including inflammation suppression, blocking of Rho kinase and

aldosterone release. Evidences shown that T- type CCBs offer more benefits on proteinuria compared to L-type CCBs in chronic kidney disease (CKD) patients.[27]

To provide renoprotective effects in CKD patients, controversy exists in the recent studies regarding preferred agents among ACEIs /ARBs (angiotensin receptor blockers) and CCBs. One of such studies demonstrated that ACEIs or ARBs have stronger renoprotective effect than that obtained with CCBs. However, the combination should be preferred.[31] In contrast, another study suggested that renoprotection achieved with ACEIs or ARBs monotherapy is equivalent to that obtained from combination therapy(ACEIs/ARBs+CCBs) and so there is no need for combination drug therapy.[32] Interestingly, a study has linked the preferred choice with the existence of proteinuria with suggestion that in case of proteinuria, preference should be given to RAAS (renin angiotensin aldosterone) blockers but L/T type CCBs would be added to the therapy when concurrent action is required. Additionally, RAAS inhibitors have not been found to be superior in hypertensive CKD patients without presence of proteinuria. Therefore, favour will be given to L/T type CCBs in such cases.[33] Furthermore, triple drug therapy with CCB, ACEI and Diuretic has been found to offer more renoprotective effects in reducing mortality risks in type II diabetic patients.[14]

5.3. Neuroprotective Actions of CCBs

5.3.1. Efficacy of CCBs in the improvement of cognitive function

Hypertensive patients are likely to have more chances of cognitive deterioration. Evidence has been reported from studies that antihypertensive therapy with CCBs lowers the occurrence of neurodegenerative events like Alzheimer's disease. The underlying mechanism is characterized by persistence of calcium homeostasis which is imbalanced in such diseases.[9] Moreover, a recent study has demonstrated that combination therapy of CCBs with SSRIs (selective serotonin reuptake inhibitors) further improves depression and cognitive function.[34]

5.3.2. Efficacy of CCBs in neuropathic pain and stroke

Like migraine, neuropathic pain is a complex symptomatic illness.[35] A strong association exists between N-type calcium channels and pathological processes involved in cerebral ischemia and neuropathic pain. Therefore, inhibition of these channels has been recommended for minimizing the neuronal injury resulting from ischemic events.[36] This is the reason, CCBs are among the evidence-based therapies for neuropathic pain.[35]

Furthermore, the neuroprotective function of CCBs makes them drugs of interest in the management of stroke.[37] Experimental ischemic models reported the neuroprotective effect of CCBs suggesting them candidates for the management of cerebral ischemia or stroke. However, the efficacy of CCBs in stroke has not been found in controlled studies.[38] Moreover, clinical trials recommend that combination therapy with RAAS inhibitors and CCBs may be useful in reducing stroke events.[39]

Table 2: A summary of protective effects of CCBs on vital bodily organs with contributing mechanisms and clinical benefits.

Protective effects	Underlying mechanisms	Clinical benefit
Cardioprotective effects	▪ Antioxidant effects via inhibition of free radical chain reaction. ▪ Inhibition of monocytes adherence towards endothelium. ▪ Inhibition of cell propagation in smooth muscles. ▪ Decline in cholesterol aggregation and esterification.	As antiatherosclerotic agents.
Reno protective effects	▪ Inhibition of L/T type and L/N type calcium channels. ▪ Inflammation suppression. ▪ Inhibition of Rho kinase and aldosterone release.	As antihypertensives in chronic kidney disease.
Neuroprotective effects	▪ Maintenance of calcium homeostasis. ▪ Inhibition of N-type calcium channels.	In neurodegenerative disorders.

6. MANAGEMENT OF RAYNAUD'S PHENOMENON

Low-moderate quality evidences have been reported from randomized controlled trials suggesting the efficacy of CCBs especially DHP group in management of Raynaud's phenomenon. They are known to minimize the duration, frequency, attacks severity and the pain and disability resulting from primary Raynaud's phenomenon (a vasospastic disease condition in which the reaction to emotion or cold is exaggerated and person shows symptoms of cyanosis, paleness in digits (fingers and toes)[41] and pain in extremities. The contributing mechanism of CCBs is vasodilation in management of Raynaud's phenomenon.

CCBs may also be effective in secondary Raynaud's phenomenon which is linked to connective tissue disorders e.g. SLE (systemic lupus erythematosus), systemic sclerosis. However, the efficacy is less than that found in primary one.[40]

7. MANAGEMENT OF GLAUCOMA

Evidence has been reported from animal studies that CCBs (Verapamil topical treatment) offer remarkable intraocular pressure reduction. However, the effect was not considerable in humans. Moreover, many hospital-based studies have demonstrated the useful effects of Brovincamine, Nilvadipine and Nimodipine on vision in normal persons. The possible mechanism suggested to be alteration of calcium influx which leads to reduction in flow of aquos humor[36] as voltage gated calcium channels are present in ciliary cells.[42]

8. USE AND SAFETY OF CALCIUM CHANNEL BLOCKERS IN OBSTETRICS

8.1. As Tocolytics

Preterm birth is a leading factor involved in perinatal morbidity and mortality. Among tocolytics, β_2 agonists are most extensively employed. However, their use is associated with unpleasant and sometimes serious maternal toxicity.[43] CCBs have been found as alternatives to other tocolytic therapies.[44] Studies have demonstrated their superiority over β_2 agonists[43] with respect to enhancement of pregnancy duration[43,51], less incidence of severe neonatal morbidity and maternal toxicity.[43] Maternal complications are found to be less associated with Nifedipine[45] than Terbutaline[46] and Nicardipine[47] with one study suggesting that Nicardipine contributes to pulmonary edema during tocolysis.[48] Nifedipine can be a 1st line treatment for management of preterm labor[49,50] owing to less toxicity profile and ease of administration compared to β-mimetics while Nicardipine should be avoided as tocolytic.[50]

8.2. Safety of CCBs in Pregnancy and Lactation

CCBs are widely employed for the management of pregnancy induced HTN.[53] Studies suggest that no major teratogenicity is associated with their use during 1st trimester of pregnancy.[54] However, due to insufficient information available, there are concerns regarding their safety in pregnancy and that is the reason, they remain unlicensed for use in pregnant ladies in various countries.[55] Moreover, no sufficient information is available supporting their safety in lactation.[53]

9. CONCLUSIONS

CCBs, a heterogenous class of antihypertensives are found to have multiple clinical applications not only in cardiovascular pharmacotherapy but also in various pathological conditions other than the cardiovascular system.

The discovery of novel CCBs is considered a breakthrough in drug research owing to their diverse protective actions on vital bodily organs (the Heart, the Brain and the Kidney), Their organ protective features can be considered in hypertensive patients for improvement in quality of life and to minimize the chances of morbidity and mortality. Such agents have pointed new areas of cardiovascular research.

Moreover, some controversies have been found in the literature regarding the effectiveness and superiority of CCBs in various disease conditions including studies suggesting the preferable choices among ACEIs or ARBs and CCBs to offer renoprotective effects in CKD patients. Similarly, uncertainty has been found regarding the beneficial effects of CCBs in the management of stroke. Studies suggesting the use of CCBs in Glaucoma management have also raised questions that whether CCBs are superior over the existing Glaucoma therapies including muscarinic agonist drugs e.g. Pilocarpine, β- blockers e.g. Timolol, carbonic anhydrase inhibitors e.g. Acetazolamide and prostaglandin agonist e.g. Lantanoprost etc. Also, there are concerns regarding CCBs use and safety in 2nd and 3rd trimesters of pregnancy and in lactation as well.

All these limitations demand further trials for the investigation of CCBs superiority over other therapies. Additionally, identification of optimal formulation dosage regimens of several types of CCBs is also required in the future trials. Moreover, the safety of CCBs in the 2nd and 3rd trimesters of pregnancy need to be evaluated.

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