IJPSR (2019), Volume 10, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 23 February 2019; received in revised form, 08 June 2019; accepted, 31 July 2019; published 01 November 2019

A COMPLETE GUIDE ON THE PHARMACOLOGIC AND PHARMACOTHERAPEUTIC ASPECTS OF CALCIUM CHANNEL BLOCKERS: AN EXTENSIVE REVIEW

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Keywords:

Novel Calcium channel blockers, Pharmacology, Pharmacokinetics, and Pharmacotherapeutics

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ABSTRACT: The calcium channel blockers, a diverse group of cardiovascular drugs, exert their action by inhibiting the L-type calcium channels and cause vasodilatation in the heart and the smooth muscles. They also block the action potential at the SA and AV node, thus prolonging the duration of the action potential (Verapamil and Diltiazem). Although, the calcium channel blockers have the same anti-hypertensive actions, they have a vast difference in their pharmacological actions, pharmacokinetic profile, and adverse reactions. The main aim was to review, compare, and understand the complete pharmacological profile of all the calcium channel blockers and understand their place in pharmacotherapy. Numerous articles and studies showed that amlodipine remains to be the safe and effective drug of choice in chronic hypertension due to its slow, prolonged duration of action and lesser incidence of reflux tachycardia. The newer calcium channel blockers, although similar to amlodipine in blood pressure lowering effect, have several pharmacological advantages. Felodipine was found to be slightly better than amlodipine in the treatment of ischemia/angina due to its high pre-load reducing the effect. Lercanidipine was found to be a better reno-protective agent than amlodipine due to its actions in the kidney. Benidipine was found to be an excellent, anti-atherosclerotic, and reno-protective agent. The incidence of baroreceptor activation and pedal edema was also found to be lower in the newer calcium channel blockers. Hence, the new generation calcium channel blockers could be preferred for various cardiovascular problems.

INTRODUCTION: History: It was identified by Fleckenstein *et al*., in the late 1960s that drugs can alter cardiac and smooth muscle contraction by blocking the entry of Ca^{2+} into the myocytes. Godfraind and his associates showed that the effect of diphenylpiperazine analogs in preventing agonist-induced vascular smooth muscle contraction could be overcome by raising the concentration of Ca^{2+} in the extracellular medium [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(11).4830-43

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(11).4830-43

Hass and Hartfelder, in 1962, identified that Verapamil, a vasodilator possesses negative inotropic and chronotropic effects that were not present with other types of Calcium channel blockers. Studies on pharmacological functions of calcium were initiated in the mid-1960s, and their therapeutic applications globally occurred in the 1980s. Verapamil was the first clinically available calcium channel blocker [2].

2. General Pharmacology: A high cytosolic calcium concentration causes increased contraction of the heart and the vascular smooth muscles [3]. Calcium generally enters the cell *via* the slow L-type calcium channels from the extracellular fluid into the cytosol, which causes an increased release of calcium from the sarcoplasmic reticulum and

mitochondria. This results in an increased Ca^{2+} level inside the cells, which in turn increases contraction and blood pressure [3-7]. Calcium channel blockers inhibit L-type calcium channels causing vasodilatation and decrease in heart rate.

In the heart, these agents reduce/ inhibit the movement of calcium through the SA and AV node, which reduces the action potential in SA and AV node and prolongs their refractoriness. The calcium channel blockers act on phase 2, which in turn inhibits phase 3 depolarization(inhibits K^+ Channels), thus inhibiting phase 4 depolarization and prolongs the duration of action potential (Verapamil and Diltiazem) [3-7].

3. Classification of Calcium Channel Blockers:

TABLE 1: CLASSIFICATION OF CALCIUM CHANNEL BLOCKERS [5, 6]

Drug	Classification
Nifedipine (Dihydropyridines)	First generation
Verapamil (Diphenylalkylamine)	First generation
Diltiazem (Benzothiazepine)	First generation
Nifedipine extended release	Second generation
Nicardipine (Dihydropyridine)	First generation
Benidipine	Second/Third generation
Amlodipine (Dihydropyridine)	Third generation
Lercanidipine (Dihydropyridine)	Third generation
Azelnidipine (Dihydropyridine)	Third generation
Felodipine, Isradipine, Nisoldipine, Nimodipine (Dihydropyridines)	Third generation
Cilnidipine (Dihydropyridine)	Fourth generation

The first generation drugs have a rapid onset of action and hence are likely to cause reflex tachycardia by baroreceptor reflex mechanism [5, 6]. These drugs reduce both myocardial contractility and the conduction of electrical impulses to the heart, but multiple dosing is required. Nifedipine immediate-release should only be used for the treatment of hypertension or chronic stable angina only if no other treatment is appropriate, due to the dose-dependent risk of cardiovascular complications and mortality [5, 6].

The second generation of drugs have a better pharmacokinetic profile and also have reduced baroreceptor activation. They are also associated with less negative inotropic effect and reduced effect on AV conduction [6].

The third generation drugs, with slow and prolonged action, limit reflux tachycardia [5, 6]. They are also associated with vast pleiotropic effects. The newer fourth-generation calcium channel blockers Cilnidipine possess both L and N-type calcium channel blocking action. Hence, these drugs can completely attenuate the activation of sympathetic system [6].

4. Mechanisms of Actions:

4.1 Pharmacodynamic Actions:

4.1. A. Vascular Tissue: In the vascular smooth muscle cells, calcium influx results in depolarization [7]. There are three mechanisms of calcium-dependent vasoconstriction that is antagonized by the Calcium channel blockers.

1. Due to depolarization, the voltage-sensitive calcium channel opens which causes a movement of calcium down the concentration gradient from the extracellular fluid into the cell, after which the channel closes and remains in the cell until the channel is opened by the next stimulus [8, 9].

2. The high intracellular calcium causes the interaction and activation of Inositol triphosphate-Protein kinase C pathway, resulting in the release of calcium from the sarcoplasmic reticulum into the cell leading to profound contraction [9].

3. Calcium interacts with calmodulin and causes phosphorylation of myosin light chain kinase. It also interacts with actin and myosin, leading to increased contractility [8, 9]. All the three steps are inhibited by the calcium channel blockers at the vascular levels.

4.1. B. Cardiac Cells: The cardiac cells depolarization is initiated by fast, rapid and short Na influx through voltage-gated sodium channels which causes a rapid upstroke, depolarization, followed by the opening of Ca^{2+} channels and the plateau phase. Within the myocardium, there exists an interaction between calcium and troponin C, which in turn permits the interaction of actin and myosin, resulting in increased myocardial contractility and heart rate [9, 10]. Calcium channel blockers inhibit the opening of calcium channels, decrease the interaction between actin and myosin and thus decreases the heart rate and myocardial contractility to a certain extent [9, 10].

5. Drug Profile of Individual Drugs:

5.1. Nifedipine:

5.1. A. Pharmacology: (The mechanism of action is similar to the action described above in sections 2 and 4).

Nifedipine belongs to the first generation Dihydropyridines and acts predominantly in the vascular smooth muscles by inhibiting the slow L-type voltage-gated calcium channels and the movement of calcium into the vessels leading to vasodilation. It also has a minor action in the cardiac myocytes, causing a reduction in myocardial contractility. Nifedipine causes a significant negative chronotropic effect with moderate negative inotropic and negative dromotropic effect.

Nifedipine produces an immediate baroreceptor reflex action that causes activation of the sympathetic system, which leads to rapid reflux tachycardia [11]. This condition occurs immediately when immediate release preparation is used and slowly in sustained release formulation.

5.1. B. Pharmacokinetics: Nifedipine is completely absorbed from the GIT and undergoes pre-systemic first pass metabolism, and hence the bioavailability varies between 55 to 75%. The Tmax for immediate release occurs at 30 min and 6 hours for sustained release. It is 95% protein bound and undergoes significant hepatic metabolism by CYP3A4 enzyme. The drug is excreted 80% by the renal route. The half-life is about 2 h for immediate release and 6 to 8 h for sustained release [12, 13].

5.1. C. Adverse Reactions:

Common: Hypotension, peripheral edema, flushing, headache, dizziness, nausea, dyspnea[14].

Serious: Reflex tachycardia, myocardial infarction, ventricular dysrhythmia, ulcers, hepatotoxicity, gingival hyperplasia and a plastic anemia [14].

5.1. D. Dosing:

Extended Release: Initial 30 or 60 mg OD, titrate to max 120 mg/day on an empty stomach [15].

Immediate Release: Initial 10 mg 3 times, maintained with 30 mg T.I.D titrated to 120 mg over 14 days (in case of hypertensive emergencies and chronic angina) [15].

5.2. Verapamil:

5.2. A. Pharmacology: Verapamil acts both on the heart and in the vascular smooth muscle. The vascular action of Verapamil is similar to the description in Section 2, 4. In the heart, Verapamil not only slows down the movement of calcium through the voltage-gated calcium channels in the SA and AV node but also prolongs their refractoriness. Verapamil binds to the L-type calcium channels, thereby inhibiting their opening and calcium influx. It also inhibits the opening of potassium channels by blocking the phase 3 repolarization and simultaneously inhibits phase 4 depolarization (inhibiting the spontaneous depolarization). It blocks the action potential at the SA and AV node, causing a negative chronotropic and inotropic effect. Verapamil reduces after load and myocardial contractility [16].

5.2. B. Pharmacokinetics: Verapamil is absorbed from the GIT and has a high hepatic extraction; hence, the bioavailability is 20%. The Tmax after an immediate release occurs at about 1.5 h whereas for sustained release it is 5 h. It is 90% protein bound and undergoes extensive hepatic metabolism by CYP3A4, CYP2D6, CYP1A2, CYP2C9, CYP2C19, demethylation and dealkylation to form active nor-verapamil. About 70% of the metabolites are eliminated by the renal route. The $t_{1/2}$ is between 3-7 h (immediate release), 8-12 h (sustained release) and it increases in geriatric patients to about 20 h [17, 18].

5.2. C. Adverse Reactions:

Common: Hypotension, edema, constipation, dyspepsia, flu-like symptoms [19, 20].

Serious: AV block, significant bradycardia, drug interactions (it is an enzyme inhibitor), Myocardial Infarction, pulmonary edema and hepatoxicity [19, 20].

5.2. D. Contraindications:

1. Wolff-Parkinson White Syndrome.
2. Cardiogenic shock.
3. Heart failure with reduced ejection fraction and LVD.
4. Av or SA block [20].

5.2. E. Drug Interactions: Verapamil is an enzyme inhibitor of CYP3A4, CYP2D6, CYP2C9,

CYP2C19, and is also an inhibitor of P-gp. Hence, Verapamil causes significant interactions with digoxin, warfarin, amiodarone, all anti-arrhythmic, azoles, antifungal, clopidogrel, Anti-tubercular drugs, carbamazepine, phenytoin. It is contraindicated with digoxin, amiodarone and warfarin [19, 20].

5.2. F. Dosing and Dose Adjustments: Paroxysmal supraventricular tachycardia, Atrial flutter, and fibrillation: 5 to 10 mg over 2 min IV followed by 40-120 mg (immediate release).

Hypertension: Initial 80 mg T.I.D titrated to 160 mg T.I.D over 4 weeks (immediate release), 120 mg to 480 mg OD (sustained release).

Angina: Initial 80 mg T.I.D titrated to 160 mg T.I.D over 4 weeks (immediate release) [21].

In the case of hepatic or renal failure, the dose should not exceed 120 mg/day. It is contraindicated in Child-Pugh C. In case of geriatric patients of age greater than 60 years; the dose should not exceed 120 mg/day for both immediate and sustained release formulations.

Diltiazem: The pharmacological actions are similar to those of Verapamil.

5.3. B. Pharmacokinetics: The bioavailability of immediate release capsule is 40% and for sustained release is 93%. The Tmax is about 4 hours for extended release. The drug is 70 to 80% protein bound and undergoes extensive hepatic metabolism by CYP450 enzymes, demethylation, and deacetylated. It does not cause significant enzyme inhibition like Verapamil and has lesser drug interactions. It is an inhibitor P-gp and is Contra-indicated with digoxin, amiodarone. It has significant interactions with clopidogrel, azoles antifungal, anti-arrhythmic. The drug is eliminated solely by the hepatic route and hence safe in renal impairment. The $t_{1/2}$ is about 3-5 h for immediate release and 9 h for sustained release [22].

5.3. C. Adverse Drug Reactions, Uses, and Contra-Indications are Similar to that of Verapamil:

5.3. D. Dose: PSVT, Atrial fibrillations: 0.25 mg/kg over 10 min then 5-15 mg/hour. Followed by 90-120 mg sustained or extended release.

Hypertension: 180 mg initially increased to 480 mg (immediate release).

Pulmonary Hypertension: 30 mg thrice daily initially to 120-480 mg/day.

Angina: ER-180 mg once daily titrated over 7 days to 360 mg [23, 24].

5.4. Amlodipine:

5.4. A. Pharmacology: Amlodipine is a classic Dihydropyridine which inhibits the slow L-type voltage-gated calcium channels, preventing their entry into the vascular and cardiac tissue. The pharmacology appears to be similar as explained above (in sections 2 and 4) [25]. Amlodipine is an extremely slow acting drug which takes about 6 hours to act; hence, it does not have negative inotropic effects [25-30]. *In-vitro* studies have shown that only higher concentrations of Amlodipine used over a long period is associated with reflux tachycardia and short term administration has no cardio depressive actions and tachycardia. Amlodipine has also shown to inhibit potassium channels, cause peripheral vasodilatation, increase myocardial oxygen supply, and increase coronary blood and hence its anti-angina/anti-ischemic action. Amlodipine is also shown to have anti-atherosclerotic effects by inhibiting collagen synthesis; however, there are no conclusive evidence to prove its anti-atherosclerotic effects. In the kidneys, Amlodipine decreases glomerular resistance, increases renal blood, decreases the activity of renin and thus increases glomerular filtration rate to a small extent, but whether these actions persist in a long term treatment is still debatable. However, Amlodipine has been the preferred drug of choice for hypertension and angina for many years because of its favorable pharmacodynamic and pharmacokinetic properties [25-34].

5.4. B. Pharmacokinetics: After oral administration, Amlodipine is slowly and completely absorbed with Tmax occurring after 6-10 h. It has a bioavailability of 60-65%. The drug is 95% protein bound and is extensively metabolized in the liver by CYP450 enzyme and through oxidative deamination. More than 75% of the metabolites are excreted in urine with a half-life of about 30-40 h, which increases to 56 h in hepatic failure, thus requiring a small dose [32-34].

5.4. C. Adverse Reaction:
Common: Peripheral edema, flushing, headache, dizziness, nausea, dyspnea, abdominal pain, dyspepsia, constipation [32-34].

Serious: Reflux tachycardia (occurs only on a long term treatment), Ventricular dysrhythmia, nervousness, conjunctivitis, gingival hyperplasia [32-34].

5.4. D. Dose: Initially, the drug has to be started at 5mg and gradually increased to 10 mg/day over 2 weeks.

Geriatric, liver, and renal failure patients should start with 2.5 mg and then be increased to 5 mg/day [32-34].

5.5. Nicardipine:
5.5. (A). Pharmacology: A first generation Dihydropyridines has similar actions to Nifedipine (similar as described in sections 2 and 4). An additional advantage of the drug is that it increases myocardial contractility and increases coronary sinus blood (exact mechanism is unknown). It also produces a dose-dependent decrease in blood pressure and peripheral vascular resistance with a mild increase in heart rate, cardiac output, and stroke volume, but no significant change in LV end-diastolic pressure and hence the use in CHF remains controversial [35].

5.5. B. Pharmacokinetics: The drug is rapidly absorbed from the GIT with a bioavailability of 35%, and a high-fat meal decreases the bioavailability to 20% [36]. The drug is 95% proteins bound and undergoes rapid and extensive hepatic metabolism by CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP2C8. It is an inhibitor of CYP3A4, CYP2D6, and CYP2C19 (hence has significant interactions with digoxin, clopidogrel, amiodarone, anti-arrhythmic, azoles, antifungal, anti-depressants, anti-tubercular drugs) [35, 36]. More than 60% is excreted by renal route with $t_{1/2}$ of about 10 h, which increases in liver disease hence requiring dose adjustments [36].

5.5. C. Adverse Reactions: Similar to Nifedipine but with less reflux tachycardia.

5.5. D. Dose:
Hypertension, Angina: Immediate release 20 mg T.I.D.

Maintenance: 20-40 mg increased after 3 days. MAX 60 mg.

Hypertensive Emergency: 5 mg/hour IV increased by 2.5 mg/hour every 5 min to max 15mg/hour [37].

5.6. Lercanidipine:
5.6. A. Pharmacology: Lercanidipine, novel third-generation CCB although has similar action (as described in sections 2 and 4) has several advantages. Lercanidipine is highly vascular selective and is highly lipophilic which causes it to accumulate and store in the cell membranes of vascular tissues which results in a slow onset of action and persistent vasodilatory effect on vascular smooth muscles. Lercanidipine causes less negative inotropism, and the incidence of reflux tachycardia is also greatly reduced.

In addition to this, it also dilates afferent and efferent arterioles to a significant extent, reduces the glomerular resistance, increases the renal blood flow causing it to be highly nephroprotectant [38]. It also has an impact on heart failure with dilated cardiomyopathy; however, its usage in heart failure is still controversial [38, 39]. Generally, in atherosclerosis, increased cholesterol in the cell membrane reduces the calcium channel antagonism, but this drug has been shown to have the highest tolerance to cholesterol, which indicates its usage in atherosclerosis [39].

Lercanidipine, also a weak T-type calcium channel blocker is shown to have neuroprotective effects by causing attenuation of oxidative stress, inflammation, and apoptosis [40].

5.6. B. Pharmacokinetics: Lercanidipine, a highly lipophilic drug, has complete absorption and Tmax occurs in 3 h. The drug has a very high membrane partition coefficient, which provides a long-lasting effect at the site of action and once a day dosing. The drug is 98% protein bound and accumulates in arteriolar cell membranes. It is metabolized by biotransformation pathways by CYP 450 enzymes undergoing significant nitroreduction, dealkylation and glucuronidation, and the metabolites are excreted through renal routes. The plasma $t_{1/2}$ is 8 h, but due to accumulation in the vascular membrane, the effect lasts up to 24 h [41].

5.6. C. Adverse Effects:

Common: Flushing, headache, vertigo, asthenia, dizziness, Edema (significantly reduced in comparison to other CCBs).

Serious: Headache, palpitations, hypokalemia, rhinitis, vertigo, and tachycardia[42].

5.6. D. Dose: Initially, 10 mg/day on an empty stomach (as food increases absorption) gradually increased to 20 mg/day[42].

5.7. Felodipine:

5.7. A. Pharmacology: Felodipine, a novel calcium channel blocker is a highly vascular selective agent (similar to Lercanidipine). The actions are similar to the descriptions in sections 2 and 4. Felodipine generally produces a greater reduction in diastolic pressure. It causes a significant reduction in systemic vascular resistance, which increases the cardiac index. A pronounced significant reduction in left ventricular end-diastolic volume was observed, causing a reduction in pulmonary artery occlusion pressure and hence the reduction in pre-load and after-load (More pronounced pre-load reduction). It also increases coronary sinus blood flow, improves myocardial oxygen demand and hence could be the drug of choice in angina. The above arguments suggest that it may be used in heart failure [43]. The drug also has a weak diuretic/natriuretic action [44].

5.7. B. Pharmacokinetics: Felodipine is completely absorbed from the gastrointestinal tract. The systemic bioavailability is 15% due to significant first-pass metabolism. The drug is 99% protein bound. The drug is exclusively accumulated in vascular sites. The drug is significantly metabolized by CYP 450 enzymes via oxidation, and 25% is excreted by renal routes. The plasma $t_{1/2}$ is about 25 h [44, 45].

5.7. C. Adverse Reactions:

Common: Flushing, headache, respiratory tract infection, flushing, edema.

Serious: Significant hypotension, tachycardia, Angina pectoris, myocardial infarction, cerebrovascular accident [45].

5.7. D. Dose: Initial, 5 mg orally OD, gradually increased to 10 mg over 2 weeks [45].

5.8. Isradipine:

5.8. A. Pharmacology: Isradipine, with a similar action to Felodipine, except that it is not lipophilic. The general action appears to be similar as described in sections 2 and 4. Isradipine is vascular selective and has a mild diuretic action. Isradipine is known to produce a significant reduction in diastolic pressure, increase the cardiac index by 30%, and decrease the systemic vascular resistance by 30%. But during a long term therapy, these effects were not significantly present, suggesting that it is not useful in the long run [46].

5.8. B. Pharmacokinetics: The bioavailability is about 90% with Tmax of 1.5 h for immediate release and 7 h for sustained release. The drug is about 95% protein bound and undergoes significant first-pass metabolism by CYP 3A4 enzyme, ring oxidation, and ester cleavage. More than 60% is eliminated through renal routes. The $t_{1/2}$ is about 8 h [47].

5.8. C. Dose: Initial 2.5 mg BD increased to 5 mg at 4 week interval [47].

5.8. D. Adverse Effects:

Common: Flushing, headache, respiratory tract infection, flushing, edema.

Serious: Significant hypotension, tachycardia, Angina pectoris, myocardial infarction, cerebrovascular accident [47].

5.9. Nisoldipine:

5.9. A. Pharmacology: Nisoldipine, a newer drug, is the most vascular selective of all the available CCBs. It reduces blood pressure without producing any negative inotropic effect. The drug available as Coat core (CC) is an extended release preparation which gradually produces its action 24 h with minimal fluctuations in plasma concentrations [48, 49]. The drug is not associated with any reflex tachycardia or sympathetic activation [48]. This drug has been proven to be equivalent in BP reduction to ACEI inhibitors. It improves cardiac function in MI and exercises performance in angina. It is the drug of choice in elderly and black patients with chronic severe hypertension [48, 49].

5.9. B. Pharmacokinetics: Nisoldipine CC is absorbed from the GIT and has a bioavailability of only 5% due to significant first-pass metabolism.

Nisoldipine is 99% protein bound. It is metabolized extensively by hepatic dehydrogenation, hydroxylation and ester cleavage by CYP 3A4 enzymes. 60 to 80% of the drug is excreted through renal routes, thus requiring dose adjustments in severe renal failure. Although the plasma half-life is 15 hours, it produces effects for 24 h [50].

5.9. C. Dose: Initial 17 mg OD on an empty stomach; titrate to 34 mg every week.

CC Tablets: Initial 20 mg OD on an empty stomach Titrate by 10 mg every week to 20 - 40 mg/day [51].

5.9. D. Adverse Reaction:
Common: Palpitation, vasodilatation, edema, respiratory infection, flushing, dizziness, and headache [51].

5.10. Nimodipine:
5.10. A. Pharmacology: Nimodipine, although L-type calcium channel blocker, has more pronounced neuroprotective effects [52]. Nimodipine is highly lipophilic, crosses the blood-brain barrier, and reaches the brain where it causes a reduction in vasospasm in subarachnoid hemorrhage. The exact mechanism of how it reduces vasospasm is not clear. However, the drug being the most lipophilic of all CCBs accumulate in cerebral arteries, results in significant vasodilatation of arteries (significant blockage of calcium entry) and causes an increase in blood flow, thereby reducing cerebral ischemia. In an ischemic patient, Nimodipine acts as an anti-oxidant by inhibiting lipid peroxidation and superoxide dismutase rather than increasing the cerebral blood flow. Generally, in Ischemia, there is a severe dysfunction of nitric oxide synthase activity. Nimodipine administered before hemorrhage does cause an inhibition in the nitric oxide activity and acts as a protectant. Nimodipine also exhibits anti-convulsive actions and is also beneficial in improving cognitive and behavioral symptoms in organic brain syndrome, thereby slowing the progression of dementia [52-57]. It is useful in cluster headache as it relieves vasospasm [55].

Nimodipine has a less pronounced cardiovascular effect, but studies have shown it lowers the blood pressure in a small group of patients, where it causes hypotension [52-57]. However, further trials are required to suggest its use in hypertension.

5.10. B. Pharmacokinetics: The drug is highly lipophilic and undergoes high first-pass metabolism, hence the bioavailability is only 13% with Tmax of 1 h. The effect of food significantly reduces bioavailability. The drug is 97-99% protein bound. The drug undergoes extensive hepatic metabolism by CYP 3A4 enzyme and is excreted through feces. The terminal half-life of the drug is about 10 h [56].

5.10. C. Dose: Initial 60 mg orally on an empty stomach every 4 hours for 21 days; therapy should begin within 96 h of hemorrhage [57]. Reduce the dose to 30 mg in case of severe hepatic impairment.

Do not administer the Drug by IV or any Other Routes: [47]
5.10. D. Adverse Reactions:
Common: Hypotension, diarrhea, and headache [58].

Serious: Heart failure, hematoma, intravascular coagulation [58].

5.11. Benidipine:
5.11. A. Pharmacology: Benidipine is a novel CCB drug blocks three calcium channels (N, L, and T). Benidipine has the highest affinity for Dihydropyridines binding site of all CCBs. Its vascular selectivity is 20 times that of amlodipine [59]. Benidipine causes very less reflex tachycardia due to N and T type calcium channel block which inhibits the catecholamine [60]. In the kidney, it dilates both afferent and efferent arterioles leading to decrease in glomerular hypertension (similar to that of Lercanidipine) [51]. Benidipine increases renal blood flow and causes potent natriuretic action. It was also shown to reduce the apoptosis of renal tubules and slows the progression of renal failure.

It also decreases proteinuria by inhibiting glomerular platelet-derived growth factor. Benidipine is shown to reduce diabetic nephropathy [61-63]. Benidipine also protects endothelium and prevents endothelial dysfunction (that occurs in heart diseases) by inhibiting lipid peroxidation and superoxide dismutase and slows down or prevents atherosclerosis. It also increases the releases of nitric oxide synthetase, which inhibits platelet aggregation and is vasodilatory. Coronary blood supply is increased in ischemic heart slowing down myocardial infarction occurrence.

Since, it prevents endothelial dysfunction and increases nitric oxide, it prevents angina. It also significantly reduces triglyceride levels due to its high free radical scavenging and inhibition of lipid peroxidation and superoxide dismutase activity [64, 65].

5.11. B. Pharmacokinetics: The drug is well absorbed after oral administration with a Tmax of 2 h (the short time for max concentration is a particular characteristic). It is highly distributed to the tissues in the liver, kidney, and plasma [66]. The drug is 99% protein bound. The drug is extensively metabolized by CYP3A4/5, and it inhibits CYP1A1, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 leading to drug interactions with warfarin, clopidogrel, amiodarone, and digoxin. The drug is excreted by renal (36%) and non-renal routes [66, 67]. The $T_{1/2}$ of the drug is about 3 h [67].

5.11. C. Dose: Initially 2 to 4 mg once a day (the drug effect lasts for a single day), increased to 8mg /day [68].

The dose should not exceed 4mg in severe hepatic impairment.

5.11. D. Adverse Reaction:
Common: Palpitations, headache, itching, rash, photosensitivity, gynecomastia [68].

Serious: Yellowing of the skin, liver dysfunction, [68].

5.12. Cilnidipine:
5.12. A. Pharmacology: Cilnidipine, a novel 4th generation CCB, is an L and N-type calcium channel blocker. It has various pleiotropic actions. Since it inhibits N-type channels, it inhibits the activation of the sympathetic nervous system, causing no reflux tachycardia [69, 70]. The drug blocks both L and N channels with equal affinity[70]. Hence, it is the preferred drug of choice for White Coat Hypertension and morning hypertension (closely associated with sympathetic activity) [71, 72]. The drug also has a better anti-ischemic action [63] since it has favorable glucose metabolism, thereby decreasing free fatty acid oxidation and decreases the oxygen demand. It also improves left ventricular function [73].

In the kidneys, it decreases proteinuria without increasing creatinine concentration (similar to Benidipine) [74]. It also improves endothelial dysfunction by increasing nitric oxide synthetase (however its free radical scavenging effects is not determined) [75]. It is associated with the least incidence of pedal edema.

5.12. B. Pharmacokinetics: Cilnidipine is rapidly absorbed with Tmax occurring in just 2 h. The drug is lipophilic and accumulates in the tissues and has a high volume of distribution and distributes to liver, kidney, and plasma significantly. The drug is 98% protein bound and is metabolized by CYP 3A4 enzyme, to a lesser extent by CYP2C19 and dehydrogenation. 20% of the drug is eliminated in the urine and the remaining 80% through feces. The half-life is about 20 h [76].

5.12. C. Adverse Reactions:
Common: Fever, rashes, GERD, increased urination, flushing, myalgia, impotence, ischemic chest pain [77].

Serious: Heart failure, liver dysfunction, hypotension, cerebral ischemia [77].

5.12. D. Dose: Initial 5 to 10 mg increased to 20 mg/day; in case of severe liver impairment, the dose should be 5 mg/day[77].

5.13. Azelnidipine:
5.13. A. Pharmacology: Azelnidipine, another novel drug, inhibits both L and T type calcium channel. The drug is highly vascular selective and is also lipophilic. The antihypertensive actions of Azelnidipine appear to be the same as that of Nifedipine. It does not cause reflex tachycardia [78].

Azelnidipine is shown to have high anti-inflammatory and anti-oxidative property (similar to Benidipine). Azelnidipine is shown to inhibit inflammatory cytokines, interleukins, and tumor necrosis factor. It is also known to have free radical scavenging property. Since, all the inflammatory cytokine, interleukins, monocytes, tumor necrosis factor are involved in the damage of endothelial cells and produce atherosclerosis and ischemia; Azelnidipine inhibits the inflammatory mediators and is shown to be effective in atherosclerosis [79].

The drug with its anti-inflammatory property is also shown to reduce urinary albumin excretion, lower glomerular pressure by dilating afferent and

efferent arteries and arterioles [80]. Azelnidipine also reduces cerebral ischemia because of its high vascular selectivity, anti-inflammatory, anti-apoptotic, anti-thrombotic properties, inhibition of catecholamine, and increased nitric oxide activity. Azelnidipine is also a mild T-type calcium blocker; hence can be used in seizure control/prophylaxis [81]. Clinical trials have also shown that Azelnidipine reduces the heart rate and decreases proteinuria by inhibiting catecholamine [82].

5.13. B. Pharmacokinetics: Azelnidipine is lipophilic, rapidly absorbed, and exhibits dose-dependent absorption with a Tmax of 3 h (dose 5-15 mg). After multiple doses, the Tmax is about 2 hours. The drug is 95% protein bound. The drug undergoes first-pass metabolism and is metabolized extensively by CYP3A4 enzymes. The drug is excreted by feces (80%) and urine (20%) with a half-life of about 16-18 h with the effect of the drug lasting up to 24 h [83].

5.13. C. Adverse Reaction:
Common: Mild headache, hot flushes, nausea, light-headedness [84].

Serious: Increase is AST/ALT levels, bilirubin levels, jaundice, and liver failure [84].

5.13. D. Dose: Initially, 8 mg/day gradually titrated at 4 week intervals to 16 mg.

The dose should be reduced for severe hepatic impairment to 8 mg [84].

5.14. Clevidipine:
5.14. A. Pharmacology: Clevidipine is an ultra-short acting vaso-selective L-type calcium channel blocker which has similar action as that of nifedipine. Clevidipine dilates arteries and arterioles alone, reduces peripheral resistance, and increases stroke volume. It is used in emergency control of hypertension, particularly before surgery. When compared to sodium nitroprusside (Used in emergency control of hypertension), the drug has better anti-ischemic properties, and it also increases renal, splanchnic blood flow to some extent. When compared to labetalol, which is also used in emergency BP control, the drug has a very short duration of action (labetalol takes about 2 h to act). It is the drug of choice for controlling BP during surgical procedures [85]. The remaining actions appear to be the same as Nifedipine immediate release.

5.14. B. Pharmacokinetics: The drug is given by IV only, is ultra-short acting, with a protein binding of 99%. It is metabolized in the blood and tissue esterase *via* hydrolysis. The half-life is about 10 min with 74% of the drug getting eliminated renally [86].

5.14. C. Adverse Reaction:
Common: Abdominal pain, nausea, vomiting, dyspepsia, headache, constipation, and acute renal failure [86].

Serious: Reflux tachycardia, Atrial fibrillation, cardiac arrest [86]. Since the drug is given through a triglyceride emulsion, it increases the triglycerides level and is not recommended in patients with high lipid profiles [86].

5.14. D. Dose: Initial 1 to 2 mg/hour IV. Maintenance 4 mg/hour.

Or

Initially, start at 1mcg/kg/min and increase at 2 min interval to 5 mcg/kg/min[86].

5.15. Lacidipine:
5.15. A. Pharmacology: Lacidipine is another novel calcium blocker has a quite similar profile to Azelnidipine. The drug differs only by its pharmacokinetic properties [87]. It also produces an anti-atherosclerotic property by inhibiting inflammatory mediators; suppress cell proliferation and suppressing the expression of matrix-metalloproteinases [88].

5.15. B. Pharmacokinetics: Lacidipine is lipophilic, experiences first pass metabolism and has a bioavailability of 10% with a Tmax of 30-120 min [79]. The drug is 95% protein bound and is metabolized by CYP450 enzymes into metabolites of which feces excrete 70%. It has a half-life of 13-19 h [89].

515. C. Adverse Reactions:
Common: Dizziness, headache, palpitations, hypotension, flushing, abdominal discomfort, and polyurea. The drug can cause tachycardia and edema at high doses [89].

Serious: Angina (on long term use) Angioedema, urticaria, extrapyramidal symptoms, gingival hyperplasia [89].

5.15. D. Dose: Initial 2 mg every morning increased at 4 week intervals to 4 mg [89]. The use of 2 mg is associated with a better adverse effect profile [89].

6. Drug Interactions of Calcium Channel Blockers: Almost all the calcium channel blockers due to extensive hepatic metabolism by CYP enzymes are generally associated with drug interactions with other enzyme inducers and inhibitors [90-92]. Of all the calcium channel blockers, Verapamil has the most drug interactions (As described earlier) [90-92].

The newer calcium channel blockers undergo hepatic metabolism by CYP450 enzymes. Hence all these drugs have drug interactions with phenytoin, carbamazepine, anti-depressants, warfarin, amiodarone, statins, anti-tubercular drugs, digoxin, amiodarone, cyclosporine requiring dosage adjustments [90-92].

DISCUSSION: The calcium channel blockers have now been a long stay in the treatment of hypertension and angina [3]. These drugs exert their actions by blocking the movement of calcium through slow voltage-gated calcium channels in the vessels as well as in the heart and decreasing the release of calcium from the sarcoplasmic reticulum, causing vasodilation. In the blood vessels, it inhibits the phosphorylation of myosin light chain kinase, inhibits the interaction between actin and myosin and in the heart inhibits the interaction between calcium and troponin C [8]. In the case of angina, it causes smooth muscle dilation and also has a negative inotropic effect on the myocardial cells of atria and the ventricles [3]. In case of arrhythmia, it inhibits the action potential at the SA and AV node (Phase 2), inhibits the opening of potassium channels and inhibiting the phase 4 depolarization and hence prolongs the duration of action potential [8].

The first and second calcium channel blockers are associated with edema, reflux tachycardia, and cardio depressive action, whereas these adverse events are reduced in the newer drugs due to its high vascular selectivity and less inotropic actions.

Numerous studies and trials have been conducted to compare the Amlodipine with Lercanidipine, Felodipine, Benidipine, and another novel CCBs. These studies have shown that the Hypertensive effects of all the drugs are almost the same. Hence, Amlodipine has now been the preferred drug for hypertension. Felodipine in comparison to Amlodipine has shown the slightly better anti-ischemic property, hence is the drug of choice in angina.

Lercanidipine has better reno-protective effects compared to Amlodipine, hence is the drug of choice for hypertension in renal failure/ risk of kidney disease [93-94]. Benidipine, compared to Amlodipine and other drugs, has excellent anti-atherosclerotic property, excellent reno-protective property, and it also decreases the progression of diabetic nephropathy. But this drug is limited for its use by severe drug interactions. The additional action of other new drugs compared to that of Amlodipine is listed in the table.

Summary of Pharmacological Actions of Calcium Channel Blockers:

TABLE 2: SUMMARY OF PHARMACOLOGICAL ACTIONS OF CCBs

Drug	Pharmacological Actions
Nifedipine	The first generation calcium channel blocker has a rapid onset of action and short duration of action, causes reflex tachycardia and hence has a limited action in MI, heart failure, and left ventricular dysfunction. Nifedipine sustained release is better tolerated
Verapamil Diltiazem	Verapamil is generally used for its anti-arrhythmic activity by blocking the action potential at the SA and AV node and prolonging the duration of action potential and the refractoriness of SA and AV node. This drug is associated with high drug interactions since it is an inhibitor of CYP enzymes and P-gp. Diltiazem exhibits similar action to Verapamil with a lower incidence of drug interactions, hence commonly used
Amlodipine	Amlodipine has similar action to that of Nifedipine, but has a very slow onset of action and prolonged duration and hence has more preferred use in hypertension and angina, since it can markedly delay the incidence of reflux tachycardia, decreases the peripheral resistance and increase the myocardial

	oxygen supply. The drug also a mild renoprotective action Amlodipine remains the drug of choice for hypertension and angina
Nicardipine	Nicardipine has actions as described in the mechanism of action section. Additionally, it increases myocardial blood flow and decreases coronary resistance. It is also associated with less incidence of reflux tachycardia. Increased drug interactions generally limit its use
Lercanidipine	Lercanidipine, a novel third-generation drug, is highly vascular selective and has lipophilicity. The drug causes persistent vasodilator effects. It has very less or nil negative inotropic action and hence no reflux tachycardia. It is considered to be highly reno-protectant, causing vasodilatation of afferent and efferent arteries and arterioles. Hence, it is the drug of choice for hypertension in renal failure
Felodipine	Felodipine is also vascular selective; causes pronounced reduction in diastolic pressure. The drug causes a significant reduction in left ventricular diastolic pressure; hence, it significantly reduces the pre-load. This is the drug of choice in ischemia/angina and also in heart failure with ischemia due to its less cardio depressive action
Nisoldipine	It is the most vascular selective of all drugs and has no reflux tachycardia. Its anti-hypertensive effect is similar to ACEI inhibitors. It is the drug of choice for blacks/black African with hypertension/angina
Nimodipine	Nimodipine, a highly lipophilic and vascular selective drug, has significant neuroprotective effects than hypertensive effects. This drug markedly reduces cerebral ischemia and increases cerebral blood flow. Hence it is the drug of choice for Hypertension with cerebral ischemia/ or risk of stroke, hypertension with dementia and hypertension with cluster headache
Benidipine	Benidipine blocks L, N, and T type calcium channels. Its hypertensive effect is similar to Amlodipine. It has similar reno-protective effects to Lercanidipine. Additionally, it has anti-atherosclerotic property, anti-inflammatory properties. It inhibits the release of catecholamine and hence does not cause reflex tachycardia. This could be the drug of choice for hypertension with atherosclerosis or risk of atherosclerosis, hypertension with Acute coronary syndrome(ACS)/ at risk of ACS, hypertension with renal failure if not for the high drug interactions with other cardiac drugs
Cilnidipine	This drug inhibits L and N channels with equal affinity and has no reflux tachycardia and SNS activity. It also has better anti-ischemic property. It is the drug of choice for white coat hypertension and bed time hypertension
Azelnidipine	This drug is a good L type and a mild T type channel blocker. It is highly lipophilic and vascular
Lacidipine	selective. This drug exhibits excellent anti-inflammatory property and a similar anti-atherosclerotic property to Benidipine. In the kidney it also offers Reno-protection. It could be the drug of choice for hypertension with inflammation of cardiac blood vessels. Lacidipine only differs in the pharmacokinetic aspects
Clevidipine	Clevidipine, an ultra-short acting drug, is used emergency control of BP before surgery. It also has a better anti-ischemic property to that of sodium nitroprusside

CONCLUSION: The calcium channel blockers have diverse pharmacological, pharmacodynamic, and pharmacokinetic action. Although, the blood pressure lowering effect of Amlodipine and other new drugs remains the same, the novel CCBS differ in their lipophilicity, vascular selectivity, pharmacodynamic properties, anti-ischemic actions, anti-atherosclerotic action, reno-protective actions, and neuroprotective actions; hence could become the preferred drug of choice in the treatment of Hypertension with angina, atherosclerosis, renal failure, cerebral ischemia, nephropathy and Coronary artery disease in the future.

ACKNOWLEDGEMENT: The author acknowledges and has a great sense of gratitude to PSG College of Pharmacy, for their continuous support and inspiration.

CONFLICT OF INTEREST: The author declared that there is no conflict of interest.

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How to cite this article:
Kishor S: A complete guide on the pharmacologic and pharmacotherapeutic aspects of calcium channel blockers: an extensive review. Int J Pharm Sci & Res 2019; 10(11): 4830-43. doi: 10.13040/IJPSR.0975-8232.10(11).4830-43.