



International Journal of Preclinical & Pharmaceutical Research

Journal homepage: www.preclinicaljournal.com

PHARMACOKINETICS AND CLINICAL EFFECTIVENESS OF CALCIUM CHANNEL BLOCKERS

Honey Sriya N^{1*}, Navya Sri N¹, Anjali A¹, Harsha Vardhini B¹, Nagaraju.M²

¹Pharm D V Year Student, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.

²Associate Professor, Department of Pharmacy Practice, KLR Pharmacy College, Paloncha, Telangana, India.

ABSTRACT

Calcium channel blockers (CCBs) are a group of medication that is extensively utilized in treatment of diverse heart disorder, such as high blood pressure, angina, and arrhythmia. These drugs work by blocking the Ca⁺ influx via the voltage-gated calcium channels, causing vasodilation, and decreased myocardial contractility and slowed heart rate. Pharmacokinetics, such as absorption, distribution, metabolism, and elimination of CCBs are of importance in their clinical efficacy. Such differences in these pharmacokinetic parameters can differ considerably with respect to their therapeutic effectiveness and side effect profiles. Selectivity between vascular smooth muscle or cardiac tissue by the drug and the response of the patient to it affects clinical effectiveness, and the selection of the agent varies depending on the exact condition of the patient. This review underscores the pharmacokinetic properties of various CCBs, the variation they have on clinical outcomes and the factors which affect their safety and efficacy in the treatment of cardiovascular diseases.

Key Words: Calcium Channel Blockers, Pharmacokinetics, Hypertension, Clinical Effectiveness, CYP3A4.

INTRODUCTION

Calcium channels are proteins that are built into the membrane, which enable the flow of calcium ions (Ca²⁺) through cell membranes and are involved in several important physiological functions. They include contraction in muscles, discharging of neurotransmitters, heartbeat regulation and neuronal functions. The division of calcium channels varies depending on its properties and distribution such as voltage-gated, ligand-gated, and store-operated channels. They also help in regulation of intracellular calcium levels which are vital in cellular homeostasis. [1] Calcium channels play a role in cellular and organ functionality because dysregulation of their activities may result in other pathophysiological conditions. Calcium channel blockers (CCBs) were discovered and transformed the management of heart diseases. First of all, CCBs were discovered as the compounds that were able to prevent the inflow of calcium ions into cells through blocking of certain calcium channels.[2] Verapamil and nifedipine which

were the first CCBs appeared during 1960s and 1970s and this was a major breakthrough in the treatment of hypertension and angina. The concept of calcium channels physiology has in the long run resulted in the creation of more selective and effective CCBs that have increased their clinical uses in the treatment of arrhythmias, heart failure, and other cardiovascular disorders [4-5] This review sets out to give a detailed analysis of the contribution of calcium channels to human physiology, the development of calcium channel blockers and their clinical application particularly in cardiovascular diseases. This review aims to outline the current developments in the field through the study of the mechanisms of action of CCBs, their clinical uses, and emerging studies. It will further delve into the predicaments and future prospects of advancing CCB therapies such as designing more specific and less side-effects agents of the newer agents to further streamline the cardiovascular disease management.[6] The calcium channel blockers may also be categorized according to their targets of calcium channels. The main targets are L-type, T-type and N-type channel, with which they contribute to various physiological processes. It is important to learn the channel-specific effects of CCBs so

Corresponding Author

Honey Sriya N

Email: nakkahoneysrija08@gmail.com

that different clinical conditions can be selected the right therapy.[7].

T-Type Calcium Channel Blockers

The T-type calcium channels are usually linked to the production of pacemaker potentials and are found in sinoatrial and other parts of the heart conduction system, mainly expressed. The channels are also involved in the process of neuronal excitability regulation and in some forms of smooth muscle contraction. T-type calcium channel blockers have less exposure to clinical practice but can potentially find a use in the management of arrhythmias and neurovascular diseases.[8,9]

N-Type Calcium Channel Blockers

The n-type calcium channels are mostly found in neurons and also in the process of neurotransmitter release. The transmission of pain can be regulated by blocking of N-type channels, and thus, N-type CCBs are subject to investigation in terms of their possible application in the treatment of chronic pain, as well as other neurological diseases. They have a lesser role in cardiovascular therapeutics than L-type CCBs, however, further studies of N-type blockers may show new therapeutic potential in pain management and neuroprotection.[10,11]

Third-Generation CCBs

The latest development in the treatment of calcium channel blockers is the third-generation CCBs. These agents are meant to provide even more selectivity and effectiveness with less adverse effects. The newer compounds under development, which provide more specific actions, fewer adverse effects on the cardiovascular system, and better patient outcomes, are the third-generation CCBs including amlodipine and newer representatives of the medication group in the treatment of hypertension, heart failure, and arrhythmias. Current research is still being conducted to enhance the therapeutic value of third-generation CCBs to a wider clinical indications.[12 -14]

$\alpha 1$ Subunit and Pore Formation

The most important structural element of the voltage-gated calcium channels is the $\alpha 1$ subunit which is the one that forms the central pore through which calcium ions pass through into the cell. This subunit is very heterogeneous, where some of the isoforms are related to the various types of VGCC (L, N, P, Q and R). [15-16] The voltage-sensing domains are found in the $\alpha 1$ subunit itself and they detect the variation in membrane potential causing the pore to open and close. Calcium ion conduction is specific and therefore 1 subunit is a major target of the drugs like calcium blockers whose goal is to control calcium influx into the cells.[17 -18]

Cardio myocytes

The L-type calcium channels are very important in the contraction of the heart muscle in cardiomyocytes. These pathways enable the influx of calcium ions into the cell when it gets depolarized which causes more calcium to get released out of the intracellular stores which is required to cause muscle contraction. These channels play an important role in the treatment of arrhythmias and heart failure because their role in the maintenance of heart rhythm and contractility is significant. The L-type calcium channels dysregulation in cardiomyocytes may result in cardiac dysfunction and arrhythmia.[19,20]

Vascular Smooth Muscle

Calcium channels play a major role in the tone of blood vessels and blood pressure in vascular smooth muscle cells. Food contraction is caused by entry of calcium ions via VGCCs especially L-type channels, which causes vasoconstriction. It is an important process that controls the vascular resistance, and therefore blood pressure. In disease-related conditions like hypertension, the excessive calcium inflow into the vascular smooth muscle cells also add to the sustained vasoconstriction and high blood pressure. [15,21] Calcium blockers are more popular in the treatment of hypertension as they block this excess calcium influx and cause vasodilation.

Neuronal Tissue

Calcium channels play a vital role in synaptic plasticity and neuron release in neuronal tissue. N-type and P/Q-type calcium channels are of particular importance in presynaptic neurons, in which they electrically mediate the release of neurotransmitters in response to membrane depolarization. These pathways are engaged in mechanisms like transmission of pain, creation of memory and regulation of mood.[22] Calcium channels Dysfunction of calcium channels in neurons can cause neurological disorders like epilepsy, chronic pain and neurodegenerative diseases. Potential therapies against such conditions are calcium channel blockers that specifically block particular types of channels.[23]

Role of Calcium in Cellular Physiology

Calcium ions are of key biochemical importance to cellular functions since they serve as a ubiquitous second messenger in many signaling routes. Intracellular calcium concentration plays a very crucial role in the functioning of the cell and is required in muscle contraction, neurotransmission, and secretion of hormones. Calcium channels, pumps and exchangers play a vital role in the regulation of calcium ions entering and leaving the cell, such that calcium signaling is properly regulated to sustain cellular activity and homeostasis.[24 -28]

Modulation of L-Type Calcium Current

The main targets of most calcium channel blockers are L-type calcium channels, the control of which is the main principle of the action of these medications. CCBs decrease calcium in the vascular smooth muscle and cardiac tissue by blocking the influx of calcium ions through these channels. The decrease in influx of calcium results in the decrease of muscle contraction which causes vasodilation and decrease in blood pressure. [29] The decreased influx of calcium in the heart lowers myocardial contractility and decelerates electrical conduction. CCBs modulation of L-type calcium current is central to the treatment of such diseases as hypertension, angina and arrhythmias where calcium regulation is central to the pathophysiology of the disease.[30]

Effects on Cardiac Tissue

CCBs exert a significant effect on vascular smooth muscle, and this is mostly by acting on L-type calcium channels. CCBs inhibit influx of calcium and encourage vasodilation, hence decreasing peripheral vascular resistance and blood pressure. The vasodilatory effect of Dihydropyridine CCBs, especially, is stronger because it is more selective to the vascular smooth muscle. [31 -35] This decrease in vascular tone is useful in the management of hypertension and angina where augmented vascular resistance may deteriorate the course of the disease. Nevertheless, vasodilation may also cause such side effects as peripheral edema in case of excessive vasodilation, and especially with long-acting dihydropyridines.

First-Pass Metabolism (CYP3A4)

The hepatic first-pass metabolism of CCBs is mainly in the liver, where they are metabolised to a large extent through the cytochrome P450 system of enzymes, specifically the CYP3A4 enzyme. This enzyme activity has a very high impact on the systemic bioavailability of numerous CCBs. As an illustration, nifedipine and diltiazem are CYP3A4 substrates and their first-pass metabolism may differ between individuals due to genetic variations or presence of co-administered drugs that can inhibit or activate CYP3A4. The heterogeneity of first-pass metabolism is a factor that clinicians should take into consideration because it can affect the dosage regimen and the treatment effect.[36]

Distribution and Protein Binding

The CCBs once absorbed are widely distributed across the body although the degree of binding with proteins varies, which influences their pharmacokinetic behavior and tissue localization. An example is drugs such as verapamil and diltiazem which are highly protein bound and a large percentage of the drug is bound to the albumin in the plasma. This binding has an influence on

the free, active concentration of drug capable of producing its therapeutic effect. Moreover, the degree of distribution may determine the effects of the drug on the target tissues such as the heart, blood vessels and smooth muscles. Protein binding may also influence drug-drug interactions and other highly protein-bound drugs may replace CCBs, raising their levels of free concentration and toxicity risk.

Sustained-Release Formulations

CCBs sustained-release preparations are intended to deliver the drug in a controlled and prolonged form over a very long period of time, keeping therapeutic plasma concentrations longer. These measures can be used to decrease the frequency of administration, increase patient adherence as well as decrease the variability of drug concentrations which may increase the therapeutic efficacy of the drug. An example of this is the sustained-release amlodipine that is commonly used in the management of chronic hypertension and angina and has the advantage of single daily dosing. [38] The creation of long-acting CCB preparations is a significant breakthrough, which enables to control cardiovascular diseases and achieve better patient outcomes due to more regular drug intake.

Cardiovascular Indications

Calcium channel blockers (CCBs) are mainly employed in the treatment of different cardiovascular diseases because they are capable of regulating the intake of calcium into the cells resulting in the following effects; vasodilation effects, lowered heart rate, lowered myocardial contractility. The use is positive in the treatment of hypertension, angina, arrhythmias, and other heart diseases. Clinical application of CCBs is more or less founded on their ability to act selectively on vascular smooth muscle or cardiac tissue, and the various subclassifications of CCBs have specific clinical benefits with respect to particular cardiovascular indications. CCBs enhance the heart performance by regulating calcium ion flux and lowering the heart workload, which is associated with improved patient outcomes in the broad spectrum of heart diseases.[39]

Hypertension

One of the most prevalent indications of the use of calcium channel blockers is hypertension, or high blood pressure. CCBs cause vasodilation (blocking calcium concentration in smooth muscle cells of blood vessels) which decrease peripheral vascular resistance, and decreases blood pressure. Amlodipine and nifedipine are some of the dihydropyridine CCBs that have strong vasodilatory properties and are therefore effective in hypertension. Verapamil and diltiazem are also non-dihydropyridine CCBs that are employed in hypertension

particularly in patients that have other conditions such as arrhythmias.

Preferred Agents in Different Populations

CCB may have different options regarding the management of hypertension based on the age of the patient, comorbidities and unique health conditions. To illustrate the point, the dihydropyridine group of amlodipine is widely used among the older adults because of its potent vasodilation and desirable side-effects. [40,41] CCBs such as amlodipine are preferred to have renal protective effects in patients with chronic kidney disease or diabetes. The non-dihydropyridines group of verapamil and diltiazem is more likely to be used in younger patients or those who are coexisting with arrhythmias due to their capability to regulate heart rate and enhance the functioning of the heart.

Combination Therapy

Taking of a combination of drugs is necessary in many hypertension patients to attain desired blood pressure control. CCBs are commonly used alongside other antihypertensive parenterals, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), or diuretics. This method may address the various routes of blood pressure control, which will have a synergistic effect and improve the overall effectiveness. The amlodipine and an ACE inhibitor can also be used together and are likely to be effective in managing blood pressure besides providing other advantages to renal protection in diabetic patients.[4,42]

Angina Pectoris

Another important indication of CCBs is angina pectoris or chest pains caused by insufficient blood supply to the heart muscle. The mechanism of action of these drugs involves the decreasing of the oxygen requirements of the myocardium by means of vasodilation thereby lowering the heart workload. CCBs come in handy especially in stable and vasospastic (Prinzmetal's) angina to relieve chest pains through enhanced blood flow to the coronary age and decreased use of myocardial oxygen.[43]

Vasospastic Angina

Prinzmetal angina, also known as vasospastic angina, is an angina that results in the blockage of the coronary arteries by spasm rather than atherosclerosis. CCBs such as diltiazem or verapamil should be used in this condition because of their capacity to inhibit or reverse coronary vasospasm by relaxing the smooth muscle of the coronary arteries. This aids in the restoration of the blood circulation and elimination of incidences of chest pains during the night or at rest.[44]

Atrial Fibrillation Rate Control

AF is a typical arrhythmia associated with increased rates of the ventricles and inadequate cardiac output. Non-dihydropyridine CCBs, in particular, diltiazem and verapamil, are prescribed to slow down the heart rate of an AF patient by decelerating AV-node conduction. These medicines have been specifically involved in rate control in AF where they reduce the ventricular response rate, which improves the symptoms and reduces cardiomyopathy caused by tachycardia.[45,46]

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is an illness that is defined by the excessive thickening of the heart muscle and may cause blood flow blockage resulting in such symptoms as shortness of breath and chest pain. Non-dihydropyridine CCBs such as verapamil help to decrease the impediment in HCM by lowering the myocardial contractility (negative inotropy) and the thickening heart muscle. These effects are used in order to enhance symptoms and avoid complications related to this condition.[47,48]

Non-Cardiovascular Indications

Besides being used to treat cardiovascular diseases, calcium channel blockers are also utilized to treat several non-cardiovascular diseases. They are effective in the treatment of smooth muscle or neuronal-related disorders due to their capability to regulate the flow of calcium in the cells. Such conditions include vascular diseases such as Raynauds syndrome to neurological diseases such as migraines and subarachnoid hemorrhage.[49]

Raynaud's phenomenon

Raynaud phenomenon is a disease that is marked by intermittent sporadic vasospasm of fingers and toes, resulting in changes of color, pain, and numbness. Nifedipine is the Dihydropyridine CCB which is used to relieve the symptoms by inducing vasodilation and enhancing blood flow to the affected areas. CCBs contribute to the reduction of vasospasm and the prevention of ischemic attacks of the Raynaud phenomenon by inhibiting the entry of calcium into the vascular smooth muscle.[51]

Peripheral Edema

Another adverse effect of the dihydropyridines CCBs, especially long acting agents such as amlodipine, is peripheral edema. This is because the peripheral blood vessels get dilated and thus cause fluid retention and swelling particularly in the lower limbs [52]. Even though usually not hazardous, peripheral edema may lead to discomfort and lack of commitment to the treatment. Treatment options are reduction of dose or replacement

by other antihypertensive agents that have lesser chances of causing edema. The side effect can be relieved in certain instances by the use of diuretics.

Flushing and Headache

The other most frequent side effects of the dihydropyridine CCBs are flushing and headache, especially in patients who are sensitive to the vasodilatory action of these medications. Flushing can be defined as a process that takes place when the blood vessels within the skin dilate to produce redness and warmth, usually around the neck and face. [53-,58] Unexpected fluctuations in blood pressure and subsequent vasodilation of cranial vessels are the determiners of headaches. The side effects are usually mild and may be overcome as time progresses, although they are irritating to some patients. When these symptoms are unresponsive

to these drugs, dose-reduction or switching to a non-dihydropyridine CCB can be taken into consideration.[60, 61]

Non-DHP Agents

The pharmacological properties of the non-dihydropyridine calcium channel blockers (CCB) are different when compared to those of dihydropyridines, since verapamil and diltiazem have different pharmacological characteristics. They act mostly on the heart and the conduction system, and thus they are useful in the treatment of arrhythmias and regulating heart rate.[62-65] Nevertheless, their activity on the cardiovascular system may cause serious side effects which are not similar to the effects of dihydropyridines. These adverse effects tend to be associated with their stronger action on cardiac functions and conduction.

Table 1: Classification of Calcium Channel Blockers (CCBs) Based on Chemical Structure

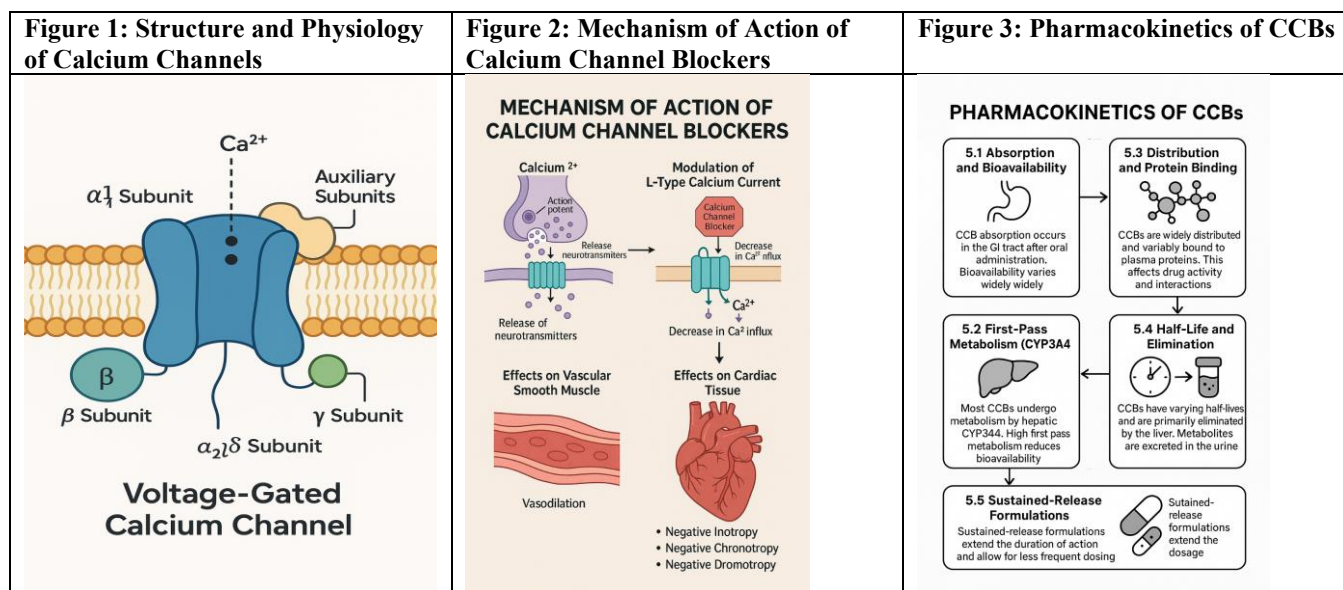
Subclass	Example Drugs	Main Action	Clinical Uses
Dihydropyridines	Amlodipine,	Act mainly on vascular smooth muscle; vasodilation	Hypertension, Angina
Phenylalkylamines	Verapamil	Target myocardium and conduction system	Arrhythmias, Hypertension
Benzothiazepines	Diltiazem	Intermediate selectivity for heart and blood vessels	Hypertension, Angina, Arrhythmias

Table 2: Classification of Calcium Channel Blockers Based on Channel Target

Channel Type	Drugs	Main Effects	Clinical Uses
L-Type	Nifedipine	Vasodilation, decreased heart rate and contractility	Hypertension, Angina, Arrhythmias
T-Type	Limited clinical use	Affect pacemaker potentials, neuronal excitability	Arrhythmias, Neurovascular diseases
N-Type	Investigational	Involved in neurotransmitter release and pain regulation	Chronic pain, Neurological conditions

Table 3: Side Effects of Dihydropyridine vs Non-Dihydropyridine CCBs

Side Effect	Dihydropyridines	Non-
Reflex Tachycardia	Common, due to vasodilation	Rare
Peripheral	Common, especially with long-acting agents	Rare
Bradycardia	Rare	Common, due to effects on heart rate
Atrioventricular Block	Rare	Possible, especially with high doses



Constipation (Verapamil)

A side effect of using verapamil, a non-DHP CCB, is constipation. Verapamil may affect the gastrointestinal tract smooth muscle causing a decrease in the motility and an increase in the transit time and therefore constipation.[66-67] The elderly patients and patients with history of gastrointestinal problems will find this side effect especially problematic. In order to control this side effect, patients can be recommended to consume more fluids and fibers or should use stool softeners or laxatives. In other instances, it may be required to change to another type of antihypertensive medications.

Gingival Hyperplasia

The overgrowth of the gum tissue or gingivitis hyperplasia is an undesirable effect of calcium channel blockers, which is rare but dangerous, especially in the case of long-term usage. This is best observed with nifedipine but may also be observed with other dihydropyridine CCBs. The proliferation of the gum tissue may cause discomfort, bleeding and difficulty in keeping the mouth clean making one prone to periodontal disease. Dental examinations and proper oral health should be conducted frequently among patients on CCBs. In extreme cases, one may need to discontinue or change to another antihypertensive agent.[68,70]

CONCLUSION

Another important pharmacokinetic factor that determines the safety and efficacy of CCBs is elimination which is mainly through the liver and kidney. As an example, half-life of CCBs is highly variable with certain ones like amlodipine possessing long half-life enabling daily intake which enhances patient compliance. Some such as nifedipine possess a shorter half-life, which requires a higher frequency of administration. Renal and

hepatic functioning affect the process of elimination, and in case of the organ malfunction, the likelihood of accumulating drugs and becoming toxic increases. Thus, patients with hepatic or renal failure usually need dose modifications, especially in the elderly population that can have decreased organ activity. The selectivity of calcium channels by CCBs is highly related to their clinical efficacy. The difference between the dihydropyridine (DHP) and non-dihydropyridine (non-DHP) CCBs plays a very important role in clinical decision-making. Dihydropyridines (like amlodipine) are generally selective to vascular smooth muscularity, and cause strong vasodilation and few impacts on the heart. This renders DHP CCBs to be useful in the treatment of hypertension and angina especially when there are no concomitant arrhythmias in a patient. Nevertheless, DHP CCBs are related to the side effects like peripheral edema owing to over-dilatation. Non-DHP CCBs such as verapami and diltiazem, on the other hand, have their action on the heart and vasodilation, decreasing myocardial contractility and heart rate, and thus are especially useful in the treatment of arrhythmia and regulation of heart rate in such conditions as atrial fibrillation. Such drugs are however associated with increased risk of side effects such as bradycardia, AV block and worsening heart failure. Pharmacodynamics also determine the effectiveness of the CCBs in the treatment of particular conditions. As an example, myocardial oxygen demand reduction resulting in vasodilation and slowed heart rate can be used successfully to relieve the chest pain in patients with stable angina. Likewise, CCBs also decrease the peripheral vascular resistance in hypertensive patients, leading to a decrease in blood pressure and cardiovascular outcome. The side effects, however, like reflex tachycardia in the dihydropyridine and constipation in the non-dihydropyridines need close monitoring in order to

achieve the best clinical performance. Further, CCBs are not applicable in heart failure because the non-DHP CCBs have a negative inotropic effect and therefore can aggravate the situation of cardiac functioning in systolic dysfunction patients. Patient specific factors which might affect the clinical efficacy of CCBs are also age, comorbidities and drug interactions. As an example, the elderly patients tend to have more side effects with CCBs since age causes alterations in the metabolism of the drug and the functioning of the organs. The comorbidities such as diabetes, chronic kidney disease, and heart failure also complicate the use of CCBs and therefore different treatment plans need to be provided to individuals. Also, polypharmacy is a frequent complication in chronic illness patients, and as such, there is a possibility of drug-drug interactions, which may either increase or decrease the action of CCBs. Close follow up, patient education and periodic adjustment should be done in order to get the best

out of CCB therapy and reduce the risks. To pharmacokinetics of calcium channel blockers are crucially important factors that define their efficacy in the clinical setting. Absorption, metabolism, distribution, and elimination may differ greatly to affect the effectiveness and safety of these medications. The knowledge of these pharmacokinetic principles enables the management of CCB therapy to individual patients in order to achieve the best results with minimal side effects. Further improvements in CCB preparations, such as the creation of more selective compounds and individualized therapy techniques regarding the pharmacogenomics, would have the capacity to improve even more the therapeutic value of the medications. Clinicians can offer a better and safer treatment of patients with cardiovascular diseases by further developing our comprehension of the pharmacokinetics and clinical use of CCBs.

REFERENCES

- Hasan AR, Tasnim F, Raihan MO, Brishti A, Aktaruzzaman M, Rayhan R, et al. The alteration of microglial calcium homeostasis in central nervous system disorders: a comprehensive review. *Neuroglia*, 5, 2024, 410-444.
- Lam CK, Wu JC, Tian L, Rhee J-W, Belbachir N, Kitani T, et al. Identifying the transcriptome signatures of calcium channel blockers in human induced pluripotent stem cell-derived cardiomyocytes. *Circ. Res.*, 125, 2019, 212-222.
- Jæger KH, Charwat V, Wall S, Healy KE, Tveito A. Do calcium channel blockers applied to cardiomyocytes cause increased channel expression resulting in reduced efficacy? *NPJ Syst. Biol. Appl.*, 10, 2024.
- Gallo G, Rubattu S, Volpe M. Angiotensin receptor blockers in the management of hypertension: a real-world perspective and current recommendations. *Vasc. Health Risk Manag.*, 18, 2022, 507-515.
- Lee EM. Calcium channel blockers for hypertension: old, but still useful. *Clin. Prev. Pharmacol.*, 5, 2023, 113-125.
- Jones KE, Meyer HR, Ballaera C, Arata WH, Dufrene K, Hayden SL, et al. The evolving role of calcium channel blockers in hypertension management: pharmacological and clinical considerations. *Curr. Issues Mol. Biol.*, 46, 2024, 6315-6327.
- Alshaya OA, Alqifari SF, Alhamed A, Alharbi S, Althewaibi S, Alshehri S, et al. Calcium channel blocker toxicity: a practical approach. *J. Multidiscip. Healthc.*, 15, 2022, 1851-1862.
- Salgado-Almario J, Vincent P, Martínez-Siela A, Molina Y, Rodríguez-García R, Vicente M, et al. ERG potassium channels and T-type calcium channels contribute to the pacemaker and atrioventricular conduction in zebrafish larvae. *Acta Physiol.*, 240, 2023.
- Qiu Q, Yang M, Gong D, Liang H, Chen T. Potassium and calcium channels in different nerve cells act as therapeutic targets in neurological disorders. *Neural Regen. Res.*, 20, 2024, 1258-1276.
- Perez-Miller S, Gomez K, Khanna R. Peptide and peptidomimetic inhibitors targeting the interaction of collapsin response mediator protein 2 with the N-type calcium channel for pain relief. *ACS Pharmacol. Transl. Sci.*, 7, 2024, 1916-1936.
- Gomez K, Santiago U, Nelson TS, Allen HN, Calderon-Rivera A, Hestehave S, et al. A peptidomimetic modulator of the CaV2.2 N-type calcium channel for chronic pain. *Proc. Natl. Acad. Sci. U.S.A.*, 120, 2023.
- Dubovsky SL. Applications of calcium channel blockers in psychiatry: pharmacokinetic and pharmacodynamic aspects of treatment of bipolar disorder. *Expert Opin. Drug Metab. Toxicol.*, 15, 2019, 35-47.
- Harrison PJ, Husain SM, Lee H, Los Angeles AD, Colbourne L, Mould A, et al. CACNA1C (CaV1.2) and other L-type calcium channels in the pathophysiology and treatment of psychiatric disorders: advances from functional genomics and pharmacoepidemiology. *Neuropharmacology*, 220, 2022, 109262.
- Guo S-J, Shi Y-Q, Zheng Y-N, Liu H, Zheng Y-L. The voltage-gated calcium channel $\alpha_2\delta$ subunit in neuropathic pain. *Mol. Neurobiol.*, 62, 2025, 2561-2572.
- Lanzetti S, Di Biase V. Small molecules as modulators of voltage-gated calcium channels in neurological disorders: state of the art and perspectives. *Molecules*, 27, 2022, 1312.
- Heck J, Palmeira Do Amaral AC, Weißbach S, El Khallouqi A, Bikbaev A, Heine M. More than a pore: how voltage-gated calcium channels act on different levels of neuronal communication regulation. *Channels*, 15, 2021, 322-338.
- Del Rivero Morfin PJ, Chavez DS, Jayaraman S, Yang L, Geisler SM, Kochiss AL, et al. A genetically encoded actuator boosts L-type calcium channel function in diverse physiological settings. *Sci. Adv.*, 10, 2024.

18. Chaigne S, Guinamard R, Benoist D, Barbeau S, Ducret T. Pathophysiological roles of the TRPV4 channel in the heart. *Cells*, 12, 2023, 1654.
19. Tomida S, Ishima T, Nagai R, Aizawa K. T-type voltage-gated calcium channels: potential regulators of smooth muscle contractility. *Int. J. Mol. Sci*, 25, 2024, 12420.
20. Beghi S, Wichapong K, Jaminon A, Schurgers LJ, Rapp N, Furmanik M, et al. Calcium signalling in heart and vessels: role of calmodulin and downstream calmodulin-dependent protein kinases. *Int. J. Mol. Sci*, 23, 2022, 16139.
21. Tan Y-Z, Fei D-D, He X-N, Dai J-M, Xu R-C, Xu X-Y, et al. L-type voltage-gated calcium channels in stem cells and tissue engineering. *Cell Prolif*, 52, 2019.
22. Trainito A, Muscarà C, Gugliandolo A, Chiricosta L, Salamone S, Pollastro F, et al. Cannabinol (CBN) influences the ion channels and synaptic-related genes in NSC-34 cell line: a transcriptomic study. *Cells*, 13, 2024, 1573.
23. Szymanowicz O, Pawlak S, Ciasłoń M, Jagodziński PP, Dorszewska J, Potocka E, et al. A review of the CACNA gene family: its role in neurological disorders. *Diseases*, 12, 2024, 90.
24. Pikor D, Hurla M, Słowikowski B, Szymanowicz O, Poszwa J, Banaszek N, et al. Calcium ions in the physiology and pathology of the central nervous system. *Int. J. Mol. Sci*, 25, 2024, 13133.
25. Johnson GA, Krishnamoorthy RR, Stankowska DL. Modulating mitochondrial calcium channels (TRPM2/MCU/NCX) as a therapeutic strategy for neurodegenerative disorders. *Front. Neurosci*, 17, 2023.
26. Sayehmiri F, Motamedi F, Batool Z, Naderi N, Shaerzadeh F, Zoghi A, et al. Mitochondrial plasticity and synaptic plasticity crosstalk: in health and Alzheimer's disease. *CNS Neurosci. Ther*, 30, 2024.
27. Reva M, Digregorio DA, Grebenkov DS. A first-passage approach to diffusion-influenced reversible binding and its insights into nanoscale signaling at the presynapse. *Sci. Rep*, 11, 2021.
28. Han C, Fu H, Zhang J, Guo L, Hui Q, Li Q, et al. Advancements in the study of synaptic plasticity and mitochondrial autophagy relationship. *J. Neurosci. Res*, 102, 2024.
29. Mesirca P, Diochot S, Torre E, Barrère-Lemaire S, Bidaud I, Lazdunski M, et al. Selective blockade of Cav1.2 ($\alpha 1C$) versus Cav1.3 ($\alpha 1D$) L-type calcium channels by the black mamba toxin calciseptine. *Nat. Commun*, 15, 2024.
30. Papa A, Marx SO, Kushner J. Adrenergic regulation of calcium channels in the heart. *Annu. Rev. Physiol*, 84, 2022, 285-306.
31. Liang L, Kung JY, Mitchelmore B, Cave A, Banh HL. Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: a systematic review and network meta-analysis. *J. Clin. Hypertens*, 24, 2022, 536-554.
32. Negru AG, Pastorici A, Crisan S, Cismaru G, Popescu FG, Luca CT. The role of hypomagnesemia in cardiac arrhythmias: a clinical perspective. *Biomedicines*, 10, 2022, 2356.
33. Cole JB, Lee SC, Prekker ME, Kunzler NM, Considine KA, Driver BE, et al. Vasodilation in patients with calcium channel blocker poisoning treated with high-dose insulin: a comparison of amlodipine versus non-dihydropyridines. *Clin. Toxicol*, 60, 2022, 1205-1213.
34. Wong A, Hoffman RS, Walsh SJ, Roberts DM, Gosselin S, Bunchman TE, et al. Extracorporeal treatment for calcium channel blocker poisoning: systematic review and recommendations from the EXTRIP workgroup. *Clin. Toxicol*, 59, 2021, 361-375.
35. Gómez-Garduño J, Soriano-Rosales RE, León-Rodríguez R, Rivera-Espinosa L, González-Ortiz A, Chávez-Pacheco JL, et al. Phytochemicals that interfere with drug metabolism and transport, modifying plasma concentration in humans and animals. *Dose Response*, 20, 2022, 155932582211204.
36. Wang X, Rao J, Zhao J, Tan Z, Yang X, Xun T. Inflammatory signaling on cytochrome P450-mediated drug metabolism in hepatocytes. *Front. Pharmacol*, 13, 2022.
37. Zhang L-K, Sun Y, Zeng H, Wang Q, Jiang X, Shang W-J, et al. Calcium channel blocker amlodipine besylate therapy is associated with reduced case fatality rate of COVID-19 patients with hypertension. *Cell Discov*, 6, 2020.
38. Wang J, Palmer BF, Vogel Anderson K, Sever P. Amlodipine in the current management of hypertension. *J. Clin. Hypertens*, 25, 2023, 801-807.
39. Mahfoud F, Wang J, Ray S. The current position of β -blockers in hypertension: guidelines and clinical practice. *Curr. Med. Res. Opin*, 40, 2024, 25-32.
40. Goicochea-Rios EDS, Chian-García AM, Gómez Goicochea NI, Yupari-Azabache IL. Factors associated with the development of chronic kidney disease in patients with arterial hypertension. *Int. J. Nephrol. Renovasc. Dis*, 17, 2024, 113-123.
41. Loutradis C, Marinaki S, Berry M, Ferro CJ, Borrow R, Sarafidis P, et al. Role of hypertension in kidney transplant recipients. *J. Hum. Hypertens*, 35, 2021, 958-969.
42. Niranjana PK, Bahadur S. Recent developments in drug targets and combination therapy for the clinical management of hypertension. *Curr. Hypertens. Rev*, 23, 2023, 226-245.

43. Rehan R, Weaver J, Yong A. Coronary vasospastic angina: a review of the pathogenesis, diagnosis, and management. *Life*, 12, 2022, 1124.
44. Lanza GA, Shimokawa H. Management of coronary artery spasm. *Eur. Cardiol*, 18, 2023.
45. Kanazawa H, Takashio S, Hoshiyama T, Ito M, Kaneko S, Kiyama T, et al. Clinical outcomes of catheter ablation for atrial fibrillation, atrial flutter, and atrial tachycardia in wild-type transthyretin amyloid cardiomyopathy: a proposed treatment strategy for catheter ablation in each arrhythmia. *Europace*, 26, 2024.
46. Mistrulli R, Ferrera A, Muthukkattil ML, Battistoni A, Gallo G, Barbato E, et al. Atrial fibrillation in patients with hypertrophic cardiomyopathy and cardiac amyloidosis: from clinical management to catheter ablation indication. *J. Clin. Med*, 13, 2024, 501.
47. Zampieri M, Stefàno P, Tomberli A, Berteotti M, Marchi A, Olivotto I, et al. Mavacamten, a novel therapeutic strategy for obstructive hypertrophic cardiomyopathy. *Curr. Cardiol. Rep*, 23, 2021.
48. Dong T, Alencherry B, Ospina S, Desai MY. Review of mavacamten for obstructive hypertrophic cardiomyopathy and future directions. *Drug Des. Devel. Ther*, 17, 2023, 1097-1106.
49. Ture HY, Lee NY, Kim NR, Nam EJ. Raynaud's phenomenon: a current update on pathogenesis, diagnostic workup, and treatment. *Vasc. Specialist Int*, 40, 2024.
50. Horak VJ, Lam S, Patel N, Abdelmageed S, Lopresti MA, Scoville J. First use of intraventricular nicardipine in a pediatric patient with vasospasm secondary to meningitis: illustrative case. *J. Neurosurg. Case Lessons*, 7, 2024.
51. Geraldini F, De Cassai A, Diana P, Correale C, Boscolo A, Zampirolo S, et al. A comparison between enteral and intravenous nimodipine in subarachnoid hemorrhage: a systematic review and network meta-analysis. *Neurocrit. Care*, 36, 2022, 1071-1079.
52. Vouri SM, Jiang X, Manini TM, Solberg LM, Pepine C, Malone DC, et al. Magnitude of and characteristics associated with the treatment of calcium channel blocker-induced lower-extremity edema with loop diuretics. *JAMA Netw. Open*, 2, 2019, e1918425.
53. Olowofela AO, Isah AO. A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria. *Ann. Afr. Med*, 16, 2017, 114.
54. Cardenas JM, Hawkins J, Newman J, Rushton W, Mendoza E, Sorabella R, et al. Central ECMO cannulation for severe dihydropyridine calcium channel blocker overdose. *JECT*, 55, 2023, 206-208.
55. Isbister GK, Jenkins S, Harris K, Downes MA, Isoardi KZ. Calcium channel blocker overdose: not all the same toxicity. *Br. J. Clin. Pharmacol*, 91, 2025, 740-747.
56. Sari YP, Candraruna DB. The potential of polysaccharides from various plants as constipation treatment. *J. Appl. Food Technol*, 10, 2023, 48-57.
57. Ikee R, Tsuru T, Yano K. Constipation in chronic kidney disease: it is time to reconsider. *Ren. Replace. Ther*, 5, 2019.
58. Mihai LL, Parlatescu I, Calin A, Burcea A. Gingival overgrowth approached using recent mechanical and laser technologies: a case report. *Exp. Ther. Med*, 27, 2024.
59. Bajkovec L, Mrzljak A, Alajbeg I, Likic R. Drug-induced gingival overgrowth in cardiovascular patients. *World J. Cardiol*, 13, 2021, 68-75.
60. Torgersen J, Mezochow AK, Newcomb CW, Carbonari DM, Hennessy S, Rentsch CT, et al. Severe acute liver injury after hepatotoxic medication initiation in real-world data. *JAMA Intern. Med*, 184, 2024, 943.
61. Wong B-S, Chiu L-Y, Tu D-G, Sheu G-T, Chan T-T. Anticancer effects of antihypertensive L-type calcium channel blockers on chemoresistant lung cancer cells via autophagy and apoptosis. *Cancer Manag. Res*, 12, 2020, 1913-1927.
62. Palanisamy S, Funes Hernandez M, Chang TI, Mahaffey KW. Cardiovascular and renal outcomes with finerenone, a selective mineralocorticoid receptor antagonist. *Cardiol. Ther*, 11, 2022, 337-354.
63. Wang Q, Liu Y, Xiang YK, Shi Q, Barbagallo F, Xu B, et al. Carvedilol induces biased β_1 adrenergic receptor-nitric oxide synthase 3-cyclic guanylyl monophosphate signalling to promote cardiac contractility. *Cardiovasc. Res*, 117, 2021, 2237-2251.
64. Cho MA, Jeong SY, Sohn I, Kim M-S, Kang JH, Paik ES, et al. Impact of angiotensin receptor blockers, beta blockers, calcium channel blockers and thiazide diuretics on survival of ovarian cancer patients. *Cancer Res. Treat*, 52, 2020, 645-654.
65. Merel SE, Paauw DS. Common drug side effects and drug-drug interactions in elderly adults in primary care. *J. Am. Geriatr. Soc*, 65, 2017, 1578-1585.
66. Parvin N, Joo SW, Mandal TK. Biodegradable and stimuli-responsive nanomaterials for targeted drug delivery in autoimmune diseases. *J. Funct. Biomater*, 16, 2025, 24.
67. Dejeu IL, Vicaş LG, Marian E, Ganea M, Frenţ OD, Maghiar PB, et al. Innovative approaches to enhancing the biomedical properties of liposomes. *Pharmaceutics*, 16, 2024, 1525.

68. McDonough CW, Cooper-Dehoff RM, Warren HR, Gong Y, Johnson JA, El Roubi NM, *et al.* Adverse cardiovascular outcomes and antihypertensive treatment: a genome-wide interaction meta-analysis in the international consortium for antihypertensive pharmacogenomics studies. *Clin. Pharmacol. Ther.*, 110, 2021, 723-732.
69. Zhao JV, Schooling CM. Using Mendelian randomization study to assess the renal effects of antihypertensive drugs. *BMC Med*, 19, 2021.
70. Yavuz S, Avcı A, Serin RG, Kaya MM, Ağaloğlu D. Effect of intravenous lipid therapy in critically ill pediatric patients with calcium channel blocker toxicity. *Turk. J. Pediatr*, 66, 2024, 75-80