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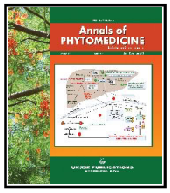

Review Article : Open Access

A systematic review of nicardipine hydrochloride

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Abstract

A common dihydropyridine calcium channel blocker with proven effectiveness in the treatment of a number of cardiovascular diseases is nicardipine hydrochloride. The goal of this systematic review is to thoroughly assess and compile the body of knowledge regarding nicardipine hydrochloride, including its safety profile, clinical indications, pharmacological characteristics, and developing research directions. After a thorough search of electronic databases, a wide variety of papers, including meta-analyses, observational studies, and randomized controlled trials, were found. A thorough analysis is conducted of the pharmacological properties of nicardipine hydrochloride, encompassing its mechanism of action, pharmacokinetics, and interactions. A comprehensive study of nicardipine hydrochloride's clinical uses in the treatment of hypertension, angina pectoris and subarachnoid hemorrhage provides insight into the drug's effectiveness and relative efficacy. A complete analysis of safety factors, including as side effects and contraindications, is conducted to offer a comprehensive understanding of the risk-benefit profile related to the usage of nicardipine hydrochloride.

1. Introduction

A calcium channel blocker of the second generation, nicardipine is used to treat stable angina pectoris and hypertension. Nicardipine therapy has not been conclusively linked to cases of clinically evident liver injury with jaundice, but it has been linked with a low rate of transient elevations in serum enzyme levels. Dihydropyridine calcium channel blockers like nicardipine hydrochloride have long been mainstays in the arsenal of cardiovascular medicine. Nicardipine hydrochloride has been extensively used to treat a number of cardiovascular diseases, such as hypertension, angina pectoris, and subarachnoid hemorrhage. It has proven to be effective in regulating calcium influx and producing vasodilatory effects. Healthcare professionals and researchers alike must have a thorough awareness of the pharmacological characteristics, therapeutic uses, and safety concerns of nicardipine hydrochloride as the field of cardiovascular medicine continues to change.

The goal of this systematic review is to offer a thorough analysis of the corpus of material that has already been written about nicardipine hydrochloride. Through the synthesis of data from a wide range of investigations, including observational analyses and randomized controlled trials, this review seeks to provide a nuanced understanding of the complex properties of nicardipine hydrochloride. By doing this, it aims to resolve important queries about its safety profile, pharmacokinetics, clinical efficacy, mechanism of action, and upcoming research trends. It is imperative to conduct a comprehensive investigation into the pharmacological and clinical characteristics of nicardipine hydrochloride due to its immense significance in the realm of cardiovascular care.

This review's opening lays the groundwork for an organized tour of the state of knowledge today, which will be built upon in the sections that follow. When we examine the many aspects of nicardipine hydrochloride, our goal is to make a meaningful contribution to the body of literature already in existence as well as to the informed decision-making processes of cardiovascular medicine researchers and practitioners (Akella Anuradha *et al*., 2023).

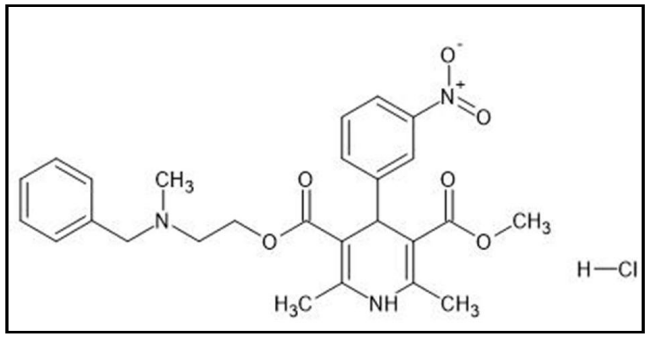

Figure 1: Structure of nicardipine hydrochloride.

2. Discovery and further history

The dihydropyridine calcium channel blocker nicardipine hydrochloride was initially created as a part of a study project to create novel substances with vasodilatory capabilities. Nicardipine's discovery can be linked to the larger investigation of dihydropyridine derivatives during the 1960s and 1970s, a time of noteworthy

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developments in cardiovascular pharmacology. The original research concentrated on comprehending the structure-activity relationship of dihydropyridines to find substances that could specifically block calcium channels in smooth muscle cells found in blood vessels. Scientists attempted to use these substance's vasodilatory properties to treat heart diseases like angina and hypertension.

During this investigation, nicardipine which has a favorable pharmacological profile became apparent as a promising candidate. High vascular selectivity and a brief duration of action are two of the distinctive qualities that set it apart from other dihydropyridines and aided in its later development as a therapeutic agent. The substance was put through a rigorous preclinical testing regimen to determine its mode of action and evaluate its safety and effectiveness. Nicardipine then moved on to clinical trials, where it proved to be beneficial in treating angina and hypertension. The medication's approval by the FDA for clinical use represented a major turning point in the field of cardiovascular pharmacotherapy.

Since going on sale, nicardipine hydrochloride has been used in several clinical contexts. Researchers and physicians are now investigating its possible advantages in conditions like perioperative hypertension and subarachnoid hemorrhage, expanding its use beyond the original indications. Research is still ongoing to find out more about the pharmacology of nicardipine and its possible therapeutic uses.

3. Physicochemical properties

Nicardipine hydrochloride's formulation, administration, and pharmacological features are influenced by its physical and chemical characteristics.

3.1 Appearance

The typical appearance of nicardipine hydrochloride is that of a white to off-white crystalline powder or solid.

3.2 Solubility

In common, nicardipine hydrochloride dissolves in organic solvents such as ethanol and methanol.

3.3 pKa

Understanding nicardipine hydrochloride's ionization properties requires knowledge of its pKa (acid dissociation constant). Certain values are 16.97 and 8.1.

3.4 Stability

Nicardipine hydrochloride needs to be kept out of direct sunlight and kept in a cool, dry location.

3.5 Odour and taste

In its pure form, nicardipine hydrochloride is usually tasteless and odorless.

3.6 Chemical formula

Nicardipine hydrochloride has the chemical formula of $C_2H_6N_{29}O_3Cl_6$.

3.7 IUPAC name

Nicardipine hydrochloride is also known as methyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate hydrochloride by the international union of pure and applied chemistry (IUPAC).

3.8 Functional groups

The presence of ester groups, nitrophenyl groups, and dihydropyridine rings in nicardipine hydrochloride is necessary for its pharmacological action.

3.9 Molecular weight

Nicardipine hydrochloride has a molecular weight of roughly 515.97 g/mol.

3.10 Melting point

Nicardipine hydrochloride has a melting point of roughly 179-182°C.

3.11 Ionization state

Nicardipine is ionized in the hydrochloride salt form, which may affect its solubility, stability, and pharmacokinetic characteristics.

3.12 Acid-base properties

Nicardipine hydrochloride can function as a weak acid, as evidenced by the presence of the hydrochloride salt.

3.13 Hydrolysis

Nicardipine hydrochloride, like many ester-containing substances, is susceptible to hydrolysis in specific situations, which can compromise its stability.

3.14 Mechanism of action

Nicardipine hydrochloride is a calcium channel blocker whose mechanism of action is based on its capacity to control the amount of calcium ions that enter cardiac and vascular smooth muscle cells. Nicardipine works as a medication by interfering with calcium ion channels. It is mostly used to treat angina pectoris and hypertension. This is a thorough description of nicardipine hydrochloride's mode of action (Pradeep Singh *et al.,* 2022).

Nicardipine is a calcium channel blocker that is a member of the dihydropyridine class. It primarily targets L-type calcium channels, which are mostly present in cardiac and vascular smooth muscle cells. Muscle contraction results from calcium ions entering the cells through these channels. Nicardipine blocks the entry of calcium ions *via* L-type calcium channels in vascular smooth muscle cells. Consequently, it lessens these cell's ability to contract, which causes the arterial blood vessels to relax and enlarge. Because of this vasodilation, blood pressure is lowered *via* a decrease in systemic vascular resistance.

Nicardipine's interaction with the heart's calcium channels can result in many different outcomes. It might have a negative inotropic effect on the force of heart muscle contraction and slow down the pace at which electrical impulses pass through the atrioventricular (AV) node. Because they lessen the heart's strain and myocardial oxygen demand, these effects may be advantageous in specific clinical circumstances, such as angina. Nicardipine can widen the coronary arteries, which provide the heart muscle with nutrition and oxygen. In cases of angina pectoris, this increased coronary blood flow can be helpful since it guarantees that the heart gets enough oxygen, which lessens the pain in the chest that is related to angina. Nicardipine effectively lowers blood pressure and reduces systemic vascular resistance in the treatment of hypertension. Since it has no discernible effect on heart rate, it is a good choice for hypertensive individuals, especially

those who also have heart issues (Subhamalar *et al.*, 2023; Amisha Sharma *et al.*, 2021).

To sum up, the main mechanism by which nicardipine hydrochloride works as a medication is by blocking L-type calcium channels in cardiac and vascular smooth muscle cells (Divya Singh *et al.,* 2023). Vasodilation, a decrease in heart workload, and a subsequent drop in blood pressure are the results of this process. Nicardipine is a useful drug for treating angina pectoris and hypertension because of these characteristics.

3.15 Method of synthesis

Nicardipine hydrochloride is synthesized through a number of steps, beginning with easily accessible starting materials. Key intermediates are usually prepared first, and then they are transformed into the finished product. Pharmaceutical companies may closely guard the specifics of their proprietary synthesis processes, but the general process for synthesizing nicardipine hydrochloride is as follows:

- Synthesis of 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyri dine
- Esterification
- Nitro group reduction
- Salt rormation
- Purification and isolation.

3.16 Medicinal uses

The main therapeutic uses of nicardipine hydrochloride, a dihydropyridine calcium channel blocker, are its vasodilatory and antihypertensive qualities. Cardiovascular disorders are the main focus of its medicinal applications.

- Excessive blood pressure, or hypertension
- Angina pectoris
- Intracranial hemorrhage
- Hypertension during surgery
- The raynaud experiments
- Heart hypertension.

3.17 Adverse drug reactions

Like any medication, nicardipine hydrochloride has the potential to cause adverse drug reactions (ADRs). People using this medication need to be aware of possible side effects and report any unusual symptoms to their healthcare provider right away. The following are a few typical nicardipine hydrochloride side effects:

- Hypotension
- Headache and flushing
- Edema in the periphery
- Palpitations or tachycardia
- Indigestion-related symptoms
- Tooth hyperplasia
- Hepatotoxicity.

3.18 Drug interaction

The majority of patients can safely take beta blockers and cardene i.v. together. When administering cardene i.v. in patients with heart failure in conjunction with a beta-blocker, warnings and precautions are to be issued (Divya Singh and Sanjeev Singh, 2021).

3.18.1 Cimetidine

When nicardipine is administered orally, it has been demonstrated that cimetidine raises the plasma concentrations of the medication. Regular checkup on patients who are taking both medications is necessary. There are no data available with other histamine-2 antagonists (Dhritimoni Devi and Sumithra, 2023; Pradeep Singh *et al.,* 2022).

3.18.2 Cyclosporine

When oral or intravenous nicardipine and cyclosporine are administered simultaneously, nicardipine inhibits hepatic microsomal enzymes, such as cyp3a4, which raises plasma levels of cyclosporine. When administering cardene i.v., keep a close eye on the plasma concentrations of cyclosporine and adjust the dosage as necessary (Vimal Raj and Sumithra, 2023).

3.18.3 Tacrolimus

When intravenous nicardipine and tacrolimus are administered simultaneously, nicardipine's inhibition of hepatic microsomal enzymes, such as cyp3a4, may raise plasma tacrolimus levels. When administering cardene i.v., keep a close eye on the tacrolimus plasma concentrations and modify the dosage as necessary (Gorman, 2002).

4. Literature review

Asplund *et al*. (1985) studied fifty patients with mild essential (primary) hypertension were randomized to receive either placebo or nicardipine 30 mg three times a day as monotherapy for six weeks in a double-blind, parallel-group study. After six weeks, the mean supine systolic/diastolic pressure in the nicardipine-treated group was statistically significantly lower at 21.2/15.0 mmHg (p<0.001) than in the placebo-treated group, which showed a nonsignificant decrease of 0.7/2.9 mmHg. Between the groups treated with nicardipine and those given a placebo, there was a significant difference in mean response (p<0.001). The mean standing systolic/diastolic blood pressure in the nicardipine-treated group decreased by 17.9/ 13.8 mmHg, a significant change (p<0.001), while the placebo-treated group experienced a change of + 3.0/-1.5 mmHg. Between the two treatment groups, there was a significant difference (p<0.001). There were only slight variations in pulse rate in both treatment groups, and there was no proof that nicardipine caused tachyphylaxis. Except for one patient who experienced muscle soreness while receiving nicardipine, all adverse events were mild. After six weeks, plasma renin activity (PRA) increased by 52% on average (p<0.01) in patients who received nicardipine. On nicardipine, there was no correlation between the initial basal or stimulated PRA and the drop in blood pressure. An efficient and well-tolerated antihypertensive medication is nicardipine (30 mg three times a day).

Francesco Amenta (2009) pointed out that nicardipine is a dihydropyridine-class calcium channel blocker (CCB) that exhibits a unique cerebrovascular profile along with potent antihypertensive action. The primary controlled clinical trials on nicardipine in conditions linked to cerebrovascular impairment have been reviewed

in this paper. CCBs are used in the management of subarachnoid hemorrhage (SAH) in order to avoid vasospasm and enhance clinical results. The CCB licensed for this indication is nimodipine. Previous research on SAH did not show a benefit of nicardipine over nimodipine. More recently, nicardipine prolonged-release implants or intra-arterially administered medication have been shown to improve clinical outcomes after severe SAH, delay ischemic deficits, and reduce the incidence of vasospasm. Nicardipine is useful in preventing stroke and is advised for high blood pressure following an acute ischemic stroke or intracerebral hemorrhage. Treatment for vascularly induced cognitive decline has been the focus of more recent research. In this context, nicardipine has been studied in over 6000 patients, and in over 60% of those treated, cognitive decline has improved. Nicardipine's antihypertensive action, safety, and efficacy in the cognitive domain point to a reconsideration of this medication's use in the treatment of vascularly induced cognitive impairment as well as in lowering the risk of recurrent stroke in patients who are already at high risk of the condition (Burnat and Robles, 1998; Ravisankar *et al*., 2014; Rao *et al*., 2008).

According to Panner Selvam *et al*. (2010) is one of the leading causes of disease-related mortality in the world is hypertension. Given that it is a chronic illness, long-term care is required. Antihypertensive medications are a prime candidate for transdermal drug delivery systems due to their drawbacks, which include variable bioavailability, extensive first- pass metabolism, and more frequent administration. This piece focuses on reviewing transdermal antihypertensive patches to improve their bioavailability and in raising the level of patient adherence (Baira Venkatesham *et al*., 2021). Timolol maleate is one of the several antihypertensive medications taken into consideration in the review, nicardipine hydrochloride, amlodipine besylate, propranolol hydrochloride, diltiazem hydrochloride, nicorandil, nitrendipine, nifedipine, lisinopril and carvedilol. The first transdermal antihypertensive medication created was clonidine. Many transdermal patches for hypertension are currently being introduced to the pharmaceutical market. For the preparation of transdermal patches, solvent evaporation or solvent casting methods were used in the majority of reported methods in the literature. Polymer, plasticizer, and penetrant concentrations were adjusted based on the amount of release needed over time (Moachon and Matinier, 1994).

Ghazyl *et al*. (2005) reported three distinct preparation techniques which were used to create inclusion complexes of nicardipine HCl (NIC) with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD): co-evaporation, kneading, and co-precipitation. The solubility method, fourier transform-infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were used to study inclusion complexation in both aqueous solution and solid state. As the concentration of cyclodextrin increased, the solubility of (NIC) increased as well, displaying Bs and AL type diagrams for (β-CD) and (HP-β-CD), respectively. The study examined and contrasted the dissolution rates of (NIC)/ cyclodextrin complexes with those of physical mixtures and pure drug. Complexation with cyclodextrins enhanced the dissolution efficiency of (NIC) to 2.8-2.9 times that of (NIC) alone. Complexation with (β-CD) increased oral bioavailability in rabbits by approximately six times (Kiran *et al*., 2019; Nageswara Rao *et al*., 2007).

5. Conclusion

Nicardipine hydrochloride's pharmacological characteristics, clinical indications, safety profile, and new research directions are all thoroughly examined in this systematic review. The medication, a calcium channel blocker based on dihydropyridine, has shown promise in treating a number of heart conditions, such as angina pectoris, hypertension, and subarachnoid hemorrhage. Examining its pharmacokinetics, clinical uses, and mechanism of action, the review sheds light on both the drug's efficacy and safety issues.

Analyzing side effects and contraindications is part of safety evaluations. Nicardipine hydrochloride's synthesis and discovery are based on the investigation of dihydropyridine derivatives, and its distinct pharmacological characteristics set it apart in the field of cardiovascular pharmacotherapy. The drug's development from initial synthesis to clinical applications is reflected in its history, highlighting its importance in cardiovascular medicine.

In the future, nicardipine hydrochloride-related topics such as innovative formulations, combination treatments, and possible off-label applications will be investigated by continuing research. This implies that efforts to maximize its therapeutic potential and broaden its applications are still ongoing. More research on the pharmacology and clinical usefulness of nicardipine is anticipated as the field of cardiovascular pharmacotherapy develops. Researchers, policy-makers, and healthcare professionals can all benefit from this systematic review. It offers a basis for comprehending the current state of knowledge regarding nicardipine hydrochloride and offers evidence-based information to assist in decision-making. To improve and broaden the drug's application in cardiovascular care, the outlook highlights the significance of continuing research. To sum up, the review advances our knowledge of nicardipine hydrochloride, enabling healthcare professionals to make well-informed decisions and opening up new directions for cardiovascular medicine research and development.

In conclusion, nicardipine hydrochloride, a dihydropyridine calcium channel blocker that is frequently used in cardiovascular medicine, is thoroughly examined in this systematic review. Nicardipine's pharmacological characteristics, such as its impact on cardiac function, vasodilatory effects, and selective calcium channel blockade, highlight its importance in the treatment of a range of cardiovascular conditions. Nicardipine hydrochloride has been shown in clinical trials to be effective in reducing blood pressure, easing the symptoms of angina, and treating certain conditions like subarachnoid hemorrhage. Its application in perioperative hypertension emphasizes its adaptability in acute environments even more. Even though, safety concerns are generally positive, they still need to be taken into account, especially in light of the possibility of hypotension, peripheral edema, and other common side effects. It is essential to be aware of these adverse reactions to make well-informed clinical decisions and manage patients. Potential uses for nicardipine hydrochloride in the future, such as novel formulations, combination therapies, and investigation of its pharmacological effects outside of established indications, are illuminated by the emerging research trends covered in this review. Nicardipine hydrochloride should be used according to the specific needs of each patient, as is the case with any medication. Close observation is necessary to guarantee the best possible therapeutic results while reducing the possibility of side effects. In summary, this review adds to the current discussion

in cardiovascular pharmacotherapy by giving a thorough analysis of nicardipine hydrochloride and educating policymakers, researchers, and clinicians alike.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Akella Anuradha; Vijey Aanandhi, M. and Afroz Patan (2023). Analyticalmethod development and validation for the simultaneous estimation of lopinavir and ritonavir by RP-HPLC method in tablet dosage form. Ann. Phytomed., **12**(1):573-580.

Amisha Sharma; Priyanka and Amarish Kumar Sharma (2021). Comparative evaluation of pathophysiology of type 1 diabetes and gestational diabetes mellitus: A review. Ann. Phytomed., **10**(1):123-131.

Asplund, J. (1985). Nicardipine hydrochloride in essential hypertension-a-controlled study. Br. J. Clin. Pharmacol., **20**(1):285-298.

Baira Venkatesham; Dandu Chaithra and Mohammed Abdul Rasheed Naikodi (2021). Pharmacognostic evaluation, physicochemical standardization and HPTLC fingerprint analysis of pomegranate (Punica granatum L.) leaf and seed. Ann. Phytomed., **10**(2):187-194.

Burnat, P. and Robles, F. (1998). High-performance liquid chromatographic determination of modafinil and its two metabolites in human plasma using solid-phase extraction. J. Chromatogr. B. Biomed. Sci. Appl., **706**(2):295-304.

Dhritimoni Devi, and Sumithra, M. (2023). Development and validation of analytical technique for the evaluation of insulin glargine by RP-HPLC, Ann. Phytomed., **12**(1):611-615.

Divya Singh and Sanjeev Singh (2021). Phytomedicine: Alternative safe vehicles on the pathway of diabetes mellitus. Ann. Phytomed., **10**(1):114-122.

Drug Bank: Nicardipine Hydrochloride https://go.drugbank.com/drugs/DB00622.

Francesco Amenta (2009). Nicardipine use in cerebrovascular disease: A review of controlled clinical studies. J. Neurol. Sci., **283**(1):219-223.

Ghazyl F. S.; Sammour, O. A. ; Ghareeb, S. A.; El-Ghamry, H. A.; Issa, M. M. and Atia, G. F. (2005). Inclusion complexes of nicardipine-HCl for oral administration, Bull. Pharm. Sci., **28**(1):119-129.

Gorman, S.H. (2002). Determination of modafinil, modafinil acid and modafinil sulfone inhuman plasma utilizing liquid-liquid extraction and high-performance liquid chromatography. J Chromatogr. B. Anal.Tech. Biomed. Life Sci., **767**(2):269-276.

Kiran; Pradeep Kumar and Simrankirti (2019). Phytochemical analysis and antioxidants activity of *Silybum marianum* (L.). Ann. Phytomed., **8**(1):127-134.

Moachon, G. and Matinier, D. (1994). Simultaneous determination of modafinil and its acid metabolism by high-performance liquid chromatography in human plasma. J.Chromatogr. B. Biomed. Appl., **654**(1):91-96.

Nageswara Rao, R.; Dhananjay, D. Shinde and Kumar, M.V.N. (2007). Development and validation of a reversed-phase liquid chromatographic method for separation and determination of related-substances of modafinil in bulk drugs. Talanta, **73**(3):407-414.

National Library of Medicines: Nicardipine Hydrochloride - Nicardipine Hydrochloride | C26H30ClN3O6 | CID 41114 - PubChem (nih.gov)

Pradeep Singh; Muhammad Arif and Sheeba Shafi (2022). *In vitro* and *ex vivo* studies to assess the antiurolithiasis activity of phenolic components of *Ricinus communis* L. and *Euphorbia hirta* L. with simultaneous HPTLC analysis. Ann. Phytomed., **11**(1):485-492.

Panner Selvam, R.; Anoop Kumar Singh and Sivakumar, T. (2010). Transdermal drug delivery systems for antihypertensive drugs: A review, Int. J. Pharm. Biomed. Res., **1**(1):1-8.

Ravisankar, P.; Gowthami, S. and Rao, G.D. (2014). A review on analytical method development. IJRPB., **2**(3):11-83.

Rao R.N.; Shinde, D.D.; Talluri, M.V.N.K and Agawane S.B. (2008). A highly sensitive and specific liquidchromatography/tandem mass spectrometric (LC–MS/MS) method for investigating the pharmacokinetics of adrafinil in rats. J.Chromatogr. B., **873**(1):119-123.

Subhamalar. K.; Vijey Aanandhi, M. and Afroz Patan (2023). Analytical method development and validation of rifaximin and ornidazole in bulk and combined tablet dosage form as per ICH guidelines, Ann. Phytomed., **12**(1):595-600.

Vimal Raj, M.; and Sumithra, M. (2023). Analysis of second-generation anti histamine fexofenadine soft gelatin capsules and its related compound by using RP-HPLC. Ann. Phytomed., **12**(1):616-627.

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