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DRUGS & CALCIUM CHANNELS: THE PAST, THE PRESENT & THE FUTURE

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ABSTRACT

Calcium channels form a significant portion of ionic channels in the human body. They are responsible for various physiological functions, the most important ones being muscle contraction, cardiac contractility, cardiac conduction and maintenance of blood vessel tonicity. Hence, these channels have always been under the microscope so as to develop drugs that will modulate their function. Agents that block these channels are being used very commonly in practice. This review focuses on the basic aspects of calcium channels and the various clinical applications of drugs affecting them.

KEYWORDS: Verapamil, Diltiazem, Dihydropyridines, Nifedipine, Amlodipine, Angina, Hypertension.

INTRODUCTION

Cardiology is one field of medicine where the physician relies heavily on drug treatment, as the conditions they treat usually need lifelong therapeutic or prophylactic pharmacotherapy. Drugs acting on calcium (Ca^{2+}) ionic channels form a major portion of the most commonly prescribed drugs in general medical practice, especially in the field of cardiology. These drugs have undergone a wide variety of changes over time, both structurally and functionally. At present, calcium channel blockers (CCBs) are being used for various conditions, and are being investigated for use in several others.

Physiological Basis: Ion channels were studied in the 1950's and were found to be useful in maintaining membrane potential, through exchange of various ions through the plasma membrane.[1] Ion channels are narrow, water-filled tunnels that are selectively permeable to specific types of ions.[2] The most common ions that are permitted through these ion channels are sodium, calcium, potassium and chloride.

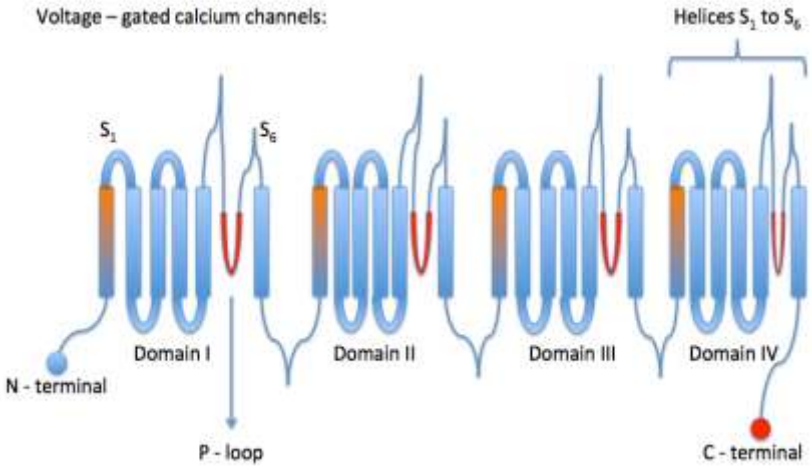
Calcium channels are a battery of ionic channels, which are grouped under these broad categories

a. Voltage gated channels
b. Ligand gated channels
c. Leaky channels

The initial classification system simply grouped the channels into two broad categories, namely, low voltage activated and high voltage activated channels.[3] Later, it was discovered that all Ca^{2+} channels could not be put under these two broad categories. Of the three current types of Ca^{2+} channels, voltage gated channels are the most clinically significant ones, and this article will mainly deal with this group of Ca^{2+} channels.

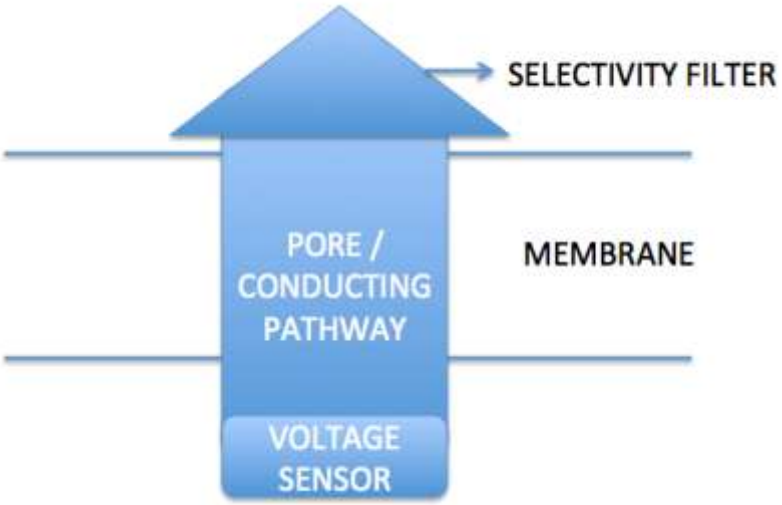
Voltage – gated calcium channels: Voltage-gated Ca^{2+} channels are structurally, funnel-shaped glycoproteins that are selectively permeable to Ca^{2+} ions across the channel, although they also admit the entry of barium ions occasionally (However, this is insignificant clinically). Earlier, these voltage-gated Ca^{2+} channels were further subdivided into three groups: L – type, T – type, and N – type. Now, two more groups have been added, namely, P/Q and R – types.[3]

Structural architecture of Ca^{2+} channels: Just like most other voltage activated channels, these Ca^{2+} channels also have a major subunit (alpha 1) and a few modulatory subunits (alpha 2, beta, gamma, delta). While the alpha unit is responsible for the functional expression of the channel, the other subunits are necessary for the kinetics and voltage selectivity of the channels. Each domain contains six membrane-spanning helices with a P-loop (Pore loop) between the last two helices (i.e., between S_5 and S_6). There are four such domains per alpha subunit, as shown in the picture 1.[4,5]



Picture 1 (Original), depicting the structural architecture of a typical Ca^{2+} channel

Functional architecture of Ca^{2+} channels



Picture 2 (Original), depicting the functional architecture of Ca^{2+} channels

Functionally, the Ca^{2+} channel consists of 3 parts: a voltage sensor, a pore or conducting pathway and a selectivity filter, as shown in the picture 2 below.[6] The selectivity filter is responsible for letting in/out of the corresponding ions and for blocking the entry/exit of all other ions.

Types of voltage-gated Ca^{2+} channels: As mentioned earlier, the voltage-gated Ca^{2+} channels are subdivided into at least five types.[3]

(a) L-type channels

These are high voltage – activated (having a conductance of 20 to 27 pS (pico Siemens)) "long – lasting" (hence called "L" type) channels that are distributed in skeletal muscles, smooth muscles, osteoblasts, ventricular myocytes, endocrine cells, etc. This subtype is the one that is targeted by clinically used calcium channel blockers. Hence they are also known as dihydropyridine receptors.[7]

(b) T-type channels

These are low voltage – activated "transient" (hence called "T" type) channels that are seen in neurons, osteocytes, pacemaker cells of the heart, placenta, lung, kidney, etc. Drugs that are clinically useful in the treatment of absence seizures target these channels.[8] Mibefradil, a calcium channel blocker that was later withdrawn from the market, also targets the T-type channels.[9]

(c) N-type channels

These channels are high voltage – activated (with a conductance of about 13pS) "neuronal" (hence called "N" type. Literature also suggests these channels could have been named after the scientist, Martha "Nowycky") channels found in plenty in the brain, peripheral nervous system and in sperm. Omega conotoxin, a toxin from marine cone snails, blocks these channels.[10] Further, ziconotide (a synthetic derivative of peptide toxin from marine cone snails), which is being evaluated for its analgesic property, also blocks these channels.[11]

(d) P/Q-type channels

They are high voltage – activated channels that are present mainly in the "Purkinje" (hence called "P" type; "Q" simply because it is the next alphabet) fibres in the cerebellum. Omega agatoxin, a toxin from spiders, blocks this type of channels.[12]

(e) R-type channels

These are intermediate voltage – activated channels that were not found to have properties matching the other four types of channels. So they are also termed "residual" channels. Also, if the Ca^{2+} blockers are applied, these channels survive the blockade. Hence, they are also known as "resistant" channels. They are mainly located in the cerebellum and sperm cells.

Drugs acting on / through calcium channels: The various drugs that act on / through Ca^{2+} channels can be grouped into three broad categories

(a) Calcium channel agonists

(b) Calcium channel blockers

(c) Calcium channel sensitizers

Calcium channel agonists

There are no clinical implications of the drugs that have agonistic activity on the Ca^{2+} channels. BayK 8644 is an agent that has agonistic activity on L-type Ca^{2+} channels. However, it is being employed only for experimental purposes and has no clinical use. The other agents that have similar activity are CGP 28 392, YC 170 and FPL 64176.[13,14]

Calcium channel blockers

Calcium channel blockers (CCBs) block the L-type voltage – activated Ca^{2+} channels. Since the ultimate result is prevention of Ca^{2+} ion entry, these agents are also called calcium entry blockers (CEBs). The blockers can be grouped into the following three groups based on their chemical structure.[15]

(a) Phenylalkylamines – Verapamil

(b) Benzothiazepines – Diltiazem

(c) Dihydropyridines (DHPs)

1. First generation – Nifedipine, Nicardipine, Isradipine

2. Second generation – Amlodipine, s-Amlodipine, Felodipine, Nisoldipine, Nimodipine, Clevidipine, Cilnidipine, Lercanidipine, Lacidipine, Benidipine, Azelnidipine

There are a few differences in the site at which these 3 groups of CCBs bind to on the alpha subunit of L-type channel, as listed below in Table I.

Table I, showing the different sites of drug action

Class of CCB	Site of binding
Phenylalkylamines	S6 of domain IV
Benzothiazepines	Between domains III and IV
Dihydropyridines	Both domains III and IV

Kinetics of CCBs: CCBs are orally well-absorbed drugs that have high first pass metabolism and high plasma protein binding. Most drugs show peak action between 1 and 3 hours after intake, the exception being long-acting CCBs like amlodipine, which shows peak action between 6 and 9 hours after intake. The other long-acting CCBs are isradipine and felodipine.

These drugs are metabolized by the liver and excreted by the kidneys. Verapamil, in particular, shows the phenomenon of auto – inhibition (of its own metabolism).[15] Clevidipine is a novel DHP that is available only as an intravenous formulation.[4]

Pharmacological actions of CCBs: The actions of CCBs are mainly limited to the heart and smooth muscles (vascular & non-vascular).

(a) Vascular smooth muscles

By blocking the voltage-sensitive Ca^{2+} channels in the vascular smooth muscles, CCBs inhibit the entry of Ca^{2+} ions, hence preventing normal vascular wall constriction. This leads to passive dilatation. This dilatation is more pronounced in the arteries as compared to that in the veins.[4]

(b) Heart

CCBs prevent the entry of Ca^{2+} into the myocardial cells. Troponin, which needs to be bound to Ca^{2+} to produce physiological contraction, is not activated. Hence, CCBs exert a negative inotropic action. On the nodal tissues of the heart, non-dihydropyridines exert an inhibitory action, while the DHPs do not have this action. Hence, there is always a reflex tachycardia seen with the use of DHPs but not with verapamil or diltiazem.[4]

(c) Non-vascular smooth muscles

CCBs can result in relaxation of other smooth muscles, especially the uterus and bronchi. This action is brought about by the same mechanism as with vasodilatation.[4]

Adverse effects of CCBs

The most commonly encountered adverse effects with the use of CCBs are headache and dizziness, majorly due to the vasodilatation caused by the agents. Another significant adverse effect, especially with the use of amlodipine, is peripheral pedal/ankle oedema (seen in 15-30% of patients), which is due to pre-capillary dilatation and reflex post-capillary constriction (The more potent s-enantiomer of amlodipine is preferred to avoid this adverse effect). Other adverse effects are tachycardia (as seen with DHPs) or bradycardia (as seen with phenylalkylamines and with benzothiazepines, as they have negative effects on nodal tissue of the cardium), orthostatic hypotension, leg cramps, skin rashes and gingival hyperplasia. These drugs might precipitate congestive heart failure or cause “coronary steal” phenomenon,

which is diversion of blood away from the ischaemic zone to vasodilatation in the normal heart vessels.[15]

Clinical applications of CCBs

(a) Angina pectoris

CCBs are given as they reduce the cardiac afterload and also prevent arterial spasms, hence leading to decrease in cardiac work. Hence, they find use in both classical as well as in variant angina.[15]

(b) Hypertension

According to the recent JNC (Joint National Committee) 8 recommendations[16], CCBs can be used as monotherapy as first line therapy in black hypertensives and in the elderly without diabetes mellitus. In India, these agents are used as monotherapy owing to the low cost, high tolerability and good efficacy. CCBs can also be used in hypertension in diabetics, but ACE (angiotensin converting enzyme) inhibitors or ARBs (Angiotensin Receptor Blockers) are first line agents.[17] Further, in cyclosporine – induced hypertension post – renal transplant, CCBs are being used as first – line therapy.[18]

(c) Cardiomyopathy

CCBs are used for their negative inotropic effect on the heart, hence lowering cardiac work.[15]

(d) Arrhythmias

The main usage of CCBs is in the pharmacotherapy of paroxysmal supraventricular tachycardia (PSVT).[15] Verapamil and diltiazem are preferred over the DHPs, as the DHPs can cause reflex tachycardia.

(e) Raynaud's phenomenon

Nifedipine, diltiazem, amlodipine and felodipine are used in this condition for their vasodilatory property.[15]

(f) Following sub-arachnoid haemorrhage

Nimodipine is preferred in this scenario as it is highly cerebroselective in its kinetics. Nicardipine has also been tried with some success.[19]

(g) Migraine

All three classes of CCBs have been evaluated for use in migraine. Also, they have been found to be useful in the management of cluster headache.[19]

(h) Mountain sickness

CCBs are mainly useful in the treatment of acute pulmonary oedema associated with mountain sickness.[19]

(i) Tocolysis[15]

As a tocolytic, nifedipine is preferred over the other CCBs.

(j) Nocturnal leg cramps[15]

Verapamil is used for this purpose, based on a few clinical trials. Nifedipine is not preferred for this use as it may itself cause muscle cramps as a side effect.

Contraindications to CCBs[19]

(a) Tight aortic stenosis
(b) Severe myocardial infarction
(c) Heart blocks (especially, non-dihydropyridines)
(d) Heart failure
(e) Unstable angina
(f) Pre-existing hypotension
(g) Wolff-Parkinson-White (WPW) syndrome
(h) Pregnancy (Relative contraindication)

Calcium channels and epilepsy

Agents that inhibit T-type Ca^{2+} current in the thalamo-cortical system of the brain (site of pathology in absence seizures) are useful as antiepileptic drugs in patients suffering from absence seizures / petit mal epilepsy. Ethosuximide, sodium valproate and zonisamide are drugs that act by this mechanism. In children less than 2 years of age, ethosuximide is preferred over valproate, as the latter is highly hepatotoxic. In older children, valproate is considered as the drug of choice.[8]

Novel / Emerging uses of drugs acting through calcium channels

(a) Migraine – CCBs are primarily used for prophylaxis of migraine. Flunarizine, a non-selective CCB, is the drug of choice among this class of drugs, as there have been several

satisfactory trial results. Verapamil and nimodipine are also being used for migraine prophylaxis[20]

(b) Analgesia – Ziconotide, a synthetic derivative of peptide toxin from marine cone snails is being tested for chronic and intractable pain.[11]

(c)Worm infestation – Praziquantel acts on a variant of calcium channels in tapeworms and flukes, and causes leakage of calcium ions from the membranes, leading to contractures, paralysis and expulsion of the worms.[21]

(d) Atherosclerosis – Studies indicate positive effects of CCBs in mild atherosclerosis. CCBs (mainly, dihydropyridines) are being tried in this case because of their propensity to slow progression of the disease[.22]

(e)Renal failure[23] – There are ongoing clinical trials to evaluate the efficacy of CCBs in renal failure, both in post-transplant and in non-transplant kidney injury patient.

(f) Parkinson's disease – Isradipine is being tried for adjuvant treatment for Parkinson's disease, as it has been postulated that CCBs can keep the dopamine-producing cells alive for a longer time, as compared to a placebo.[24]

(g) Cancer – Verapamil might be useful as an adjuvant in cancer chemotherapy, as it may reverse the resistance developed against the chemotherapeutic agents.[25] This could be due to a decrease in the calmodulin activity, leading to loss of extrusion of the anticancer drug from the resistant cells.

(h) Malaria[4] – Verapamil has been tried with some success in reversal of resistance to antimalarial agents. The mechanism could be related to p-glycoprotein and other efflux pumps.

(i) Glaucoma – CCBs might find use in attenuation of disease progression in cases of glaucoma, as evidenced by a study conducted on verapamil. Stress-induced extracellular matrix gene response was found to be reduced with verapamil pre-treatment in the lamina cribrosa cells of the optic nerve head.[26]

(j) Pulmonary artery hypertension (PAH) – CCBs are used in PAH in view of their vasodilatory property. However, they are said to be useful only in "responders" who are highly and immediately responsive to venodilatory therapy.[27]

(k) Fibrotic lung disease – CCBs might be of therapeutic usefulness in treatment or prevention of fibrotic lung disease. Animal studies on bleomycin-induced lung fibrosis have shown significant response to CCBs. This response was not due to anti-inflammatory property, but secondary to alteration of the profibrotic response to bleomycin usage.[28]

(l) Antiplatelet activity – Nifedipine is known to have an antiplatelet activity, although the mechanism involved is unclear. The hypothesis is that nifedipine can activate PPAR (Peroxisome Proliferator Activated Receptors) and result in antiplatelet action.[29]

(m)Achalasia cardia – CCBs have been tried in achalasia cardia. Nifedipine was given as primary treatment in a clinical trial but with no satisfactory results.[30]

(n) Testicular torsion-detorsion injury – Animal studies have been conducted for the effectiveness of CCBs (nifedipine) in torsion-detorsion injury of testes in rats. Encouraging results were obtained.[31]

(o) Mental depression – Flunarizine has been shown to have antidepressant action in a recent preclinical study performed on albino rats.[32]

(p) Anal fissure – CCBs have been tried with success as a modality of medical sphincterectomy in chronic anal fissures. Topical nifedipine has been found to have good therapeutic value.[33]

There are a few other studies and trials on the usefulness of CCBs in the treatment of osteoporosis, immune modulation, infertility, male contraception and schistosomiasis. However, CCBs are not approved for these uses yet.

Toxicity of CCBs

CCB toxicity is very rare. If it does occur, the effects are usually an extension of their pharmacological actions. In case of minor or trivial toxicity, the common spectrum of features seen includes flushing, dizziness, nausea and peripheral oedema. In such circumstances, discontinuation of the CCBs is not warranted. In more severe cases, direct

cardiac depression can occur, leading to bradycardia, AV block and cardiac arrest. Management of CCB toxicity has been done with high dose insulin and extracorporeal life support. Calcium, dopamine and norepinephrine have also been used in management of the same.[34]

Calcium sensitizers

Levosimendan and pimobendan are two agents that sensitize Ca^{2+} channels, and hence are clinically relevant. They do not increase the levels of Ca^{2+} in the cells, but only sensitize the receptor or end organ to the already-available Ca^{2+} ions. Levosimendan is more commonly used of the two. The main clinical applications are in refractory heart failure and refractory pulmonary hypertension. The main advantage over other drugs used in heart failure is that levosimendan does not increase the intracellular levels of Ca^{2+}, hence minimizing the risk of arrhythmias. Also, there are no significant drug-to-drug interactions, and this drug can also be tried as a "once weekly" therapy regimen, as evidenced by several trials. On the downside, the drug is very expensive, and not many studies to support its safety are available.[35,36]

REFERENCES

1. Hacker M, Messer W, Bachmann K. Ion Channels. Pharmacology: Principles and Practice. Elsevier Inc. 2009; 424.
2. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson J. How Drugs Act. Rang and Dale's Pharmacology. Elsevier Inc. 7th edition, 2012; 43.
3. McCleskey EW, Fox AP, Feldman D, Tsien RW. Different types of calcium channels. J. Exp. Biol. 1986; 124: 177-90.
4. Brunton L, Chabner B, Knollman B. Pharmacodynamics: Molecular Mechanisms of Drug Action. Goodman & Gilman's The Pharmacological Basis of Therapeutics. The McGraw Hill Companies Inc. 12th edition; 2011.
5. Lacinova L. Voltage-dependent calcium channels. Gen Physiol Biophys. 2005 Jun; 24 Suppl 1: 1-78.
6. Cain SM, Snutch TP. Voltage-Gated Calcium Channels in Epilepsy. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Available from: http://www.ncbi.nlm.nih.gov/books/NBK98147/.
7. Triggle DJ. L type Calcium channels. Curr Pharm Des. 2006; 12(4): 443-57.

8. Cheong E, Shin HS. T-type Ca^{2+} channels in absence epilepsy. Biochim Biophys Acta. 2013 Jul; 1828(7): 1560-71.
9. Martin RL, Lee JH, Cribba LL, Perez-Reyes E, Hanck DA. Mibefradil block of cloned T-type calcium channels. J Pharmacol Exp Ther. 2000 Oct; 295(1): 302-8.
10. Nielsen KJ, Schroeder T, Lewis R. Structure-activity relationships of omega-conotoxins at N-type voltage-sensitive calcium channels. J Mol Recognit. 2000 Mar-Apr; 13(2): 55-70.
11. Atanassoff PG, Hartmansgrubber MW, Thrasher J, Wermeling D, Longton W, Gaeta R et al. Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain. Reg Anesth Pain Med. 2000 May-Jun; 25(3): 274-8.
12. Teramoto T, Niidome T, Miyagawa T, Nishizawa Y, Katayama K, Sawada K. Two types of calcium channels sensitive to omega-agatoxin- TK in cultured rat hippocampal neurones. Neuroreport. 1995 Aug 21; 6(12): 1684-8.
13. Ichida S, Ariyoshi S, Fujisue T, Wada T, Akimoto T. Effects of calcium channel agonists (Bay K 8644, CGP 28392 and YC-170) on 45Ca uptake by rat uterine segments. Jpn J Pharmacol. 1991 Aug; 56(4): 397-402.
14. Rampe D, Anderson B, Rapien-Pryor V, Li T, Dage RC. Comparison of the in vitro and in vivo cardiovascular effects of two structurally distinct Ca++ channel activators, BAY K 8644 and FPL 64176. J Pharmacol Exp Ther. 1993 Jun; 265(3): 1125-30.
15. Tripathi KD. Antianginal and other anti-ischaemic drugs. Essentials of Medical Pharmacology. Jaypee Publishers. 7th edition; 2013: 546-51.
16. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014 Feb 5; 311(5): 507-20.
17. Cordonnier DJ, Zaoui P, Halimi S. Role of ACE inhibitors in patients with diabetes mellitus. Drugs. 2001; 61(13): 1883-92.
18. Cross NB, Webster AC, Masson P, O' Connell PJ, Craig JC. Antihypertensive treatment for kidney transplant recipients. Cochrane Database Syst Rev. 2009 Jul 8; (3): CD003598.
19. Satoskar RS, Rege NN, Bhandarkar SD. Pharmacotherapy of Angina pectoris, acute MI and peripheral vascular diseases. Pharmacology and Pharmacotherapeutics. Popular Prakashan Pvt. Ltd. Revised 23rd edition; 2013: 408-9.
20. Greenberg DA. Calcium channel antagonists and the treatment of migraine. Clin Neuropharmacol. 1986; 9(4): 311-28.

21. Greenberg RM. Ca^{2+} signaling, voltage-gated Ca^{2+} channels and praziquantel in flatworm musculature. Parasitology. 2005; 131 Suppl: S97-108.
22. Ishii N, Matsumura T, Shimoda S, Araki E. Anti-atherosclerotic potential of dihydropyridine calcium channel blockers. J Atheroscler Thromb. 2012; 19(8): 693-704.
23. Chan L, Schrier RW. Effects of calcium channel blockers on renal function. Annu Rev Med. 1990; 41: 289-302.
24. Parkinson Study Group. Phase II Safety, Tolerability, and dose selection study of isradipine as a potential disease-modifying intervention in early Parkinson's disease (STEADY-PD). Mov Disord. 2013 Nov; 28(13): 1823-31.
25. Simpson WG. The calcium channel blocker verapamil and cancer chemotherapy. Cell Calcium. 1985 Dec; 6(6): 449-67.
26. Quill B, Irnaten M, Docherty NG, McElnea EM, Wallace DM, Clark AF et al. Calcium channel blockade reduces mechanical strain-induced extracellular matrix gene response in lamina cribrosa cells. Br J Ophthalmol. 2015 Mar 20.
27. Medarov BI, Judson MA. The role of calcium channel blockers for the treatment of pulmonary arterial hypertension: How much do we actually know and how could they be positioned today? Respir Med. 2015 Jan 24.
28. Mukherjee S, Ayaub E, Murphy J, Lu C, Kolb M, Ask K et al. Nifedipine Disrupts Signaling in Fibroblasts and Attenuates Bleomycin-Induced Fibrosis. Am J Respir Cell Mol Biol. 2015 Feb 9.
29. Chou TC. New mechanisms of antiplatelet activity of nifedipine, an L-type calcium channel blocker. Biomedicine (Taipei). 2014; 4: 24.
30. Yesawy MI. Diagnosis and treatment of achalasia patients: a ten-year review of the clinical features. Hepatogastroenterology. 2014 Sep; 61(134): 1611-6.
31. Mestrovic J, Drmic-Hofman I, Pogorelic Z, Vilovic K, Supe-Domic D, Seselja-PerisinA et al. Beneficial effect of nifedipine on testicular torsion-detorsion injury in rats. Urology. 2014 Nov; 84(5): 1194-8.
32. Shinde V, Yegnanarayan R, Shah P, Gupta A, Pophale P. Antidepressant-like activity of flunarizine in modified tail suspension test in rats. N Am J Med Sci. 2015; 7(3): 100-3.
33. Golfam F, Golfam P, Golfam B, Pahlevani P. Comparison of topical nifedipine with oral nifedipine for treatment of anal fissure: A randomized controlled trial. Iran Red Crescent Med J. 2014; 16(8): e13592.

34. St-Onge M, Dube PA, Gosselin S, Guimont C, Godwin J, Archambault PM et al. Treatment for calcium channel blocker poisoning: A systematic review. Clin Toxicol (Phila). 2014; 52(9): 926-44.
35. Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol. 1995; 26 Suppl 1: S10-9.
36. Pierrakos C, Velissaris D, Franchi F, Muzzi L, Karanikolas M, Scolletta S. Levosimendan in critical illness: A Literature Review. J Clin Med Res. 2014 Apr; 6(2): 75-85.