Indian J Physiol Pharmacol 1991; 35(4): 217-231

CALCIUM CHANNELS AND CALCIUM CHANNEL BLOCKERS

S. D. SETH* AND SANDEEP SETH**

Departments of Pharmacology Medicine***
All India Institute of Medical Sciences,
New Delhi - 110 029

INTRODUCTION

Calcium channel blockers (CCB) have been used extensively in various cardiovascular conditions including ischemic heart disease, supraventricular arrhythmias, systemic hypertension, pulmonary hypertension, congestive heart failure and hypertrophic cardiomyopathy. They may have a role in many non-cardiac diseases like bronchial asthma, esophageal spasm, migraine, Raynaud's phenomenon and premature labor (1).

Hass and Hartfelder reported in 1962 that verapamil, a coronary vasodilator, had a negative inotropic action. Subsequently, Fleckenstein suggested that this was due to inhibition of excitation-contraction coupling via a reduction of movement of calcium ions into cardiac muscle cells (2). Rougier et al (3), presented evidence suggesting that fast and slow channels were involved in the genesis of atrial depolarization. When the transmembrane potential of a cardiac cell exceeds threshold, the 'fast channel' for 'Na^+ influx' opens up. A second inward current due to Ca^{2+} influx takes much longer to reach maximum values and is termed the 'slow channel' or 'Ca^{2+} channel'.

Calcium and Calcium Channels: Calcium in the cells can serve two functions. One, it can carry charge resulting in depolarization which can serve as a regulator of pacemaker activity or conduction velocity. The sinoatrial and the atrioventricular nodes in the heart are examples of the depolarization function of a calcium current. Two, the calcium influx can serve as an intracellular messenger. Examples of this effect in the cardiovascular system include contractile element activation by the binding of calcium to troponin in the heart and binding of calcium to calmodulin to activate myosin light-chain kinase in vascular smooth muscle.

In the study of vascular smooth muscle, two classifications of mechanisms regulating calcium influx were the voltage-dependent and receptor-operated mechanisms. The former was often studied by depolarization of vascular smooth muscle with potassium (e.g. 60mM) and the latter by stimulation of calcium influx by norepinephrine binding to post-junctional α-receptors. Now, it is recognized that voltage-dependent and receptor-operated mechanisms for increasing intracellular calcium concentration are not as discrete and simple as previously thought but are rather more complex. This has become increasingly apparent as the role of calcium as an intracellular messenger has been defined in a number of non-cardiovascular tissues. Lots of information has been gathered regarding the regulation of intracellular calcium ion concentration by studying stimulus-secretion coupling of neural and endocrine cells and the mechanisms involved in receptor-regulated metabolic processes in non-excitable organs.

Calcium Channels: The voltage dependent and receptor-operated processes form two ends of a spectrum. There are pure voltage-dependent calcium channels and also a variety of receptor-regulated mechanisms.

Receptor-agonist interaction can cause Ca^{2+} concentration to increase in the following ways: 1) receptor stimulation leads to the liberation of an intracellular messenger leading to release of calcium from intracellular storage sites, 2) receptor stimulation facilitates calcium influx through a voltage-dependent calcium channel and 3) receptor stimulation results in the coupling to and activation of a calcium channel.

*Corresponding Author

Calcium channels are divided into 3 groups: Receptor operated, stretch operated and voltage regulated calcium channels.

(i) *Receptor operated channels:* These channels increase calcium influx in response to various hormones and neuro-hormones.

(ii) *Stretch operated channels:* These are present in blood vessels and increase calcium influx on being stretched.

(iii) *Voltage-regulated calcium channels:* These are influenced by high K^+ levels or depolarizing external stimuli. Voltage sensitive calcium channels contain domains or subunits of homologous sequence that are arranged in tandem within a large subunit. These domains contain several hydrophilic regions spanning the cell membrane. Besides this main subunit termed α_1, other associated subunits include α_2, β_2, γ and δ (4).

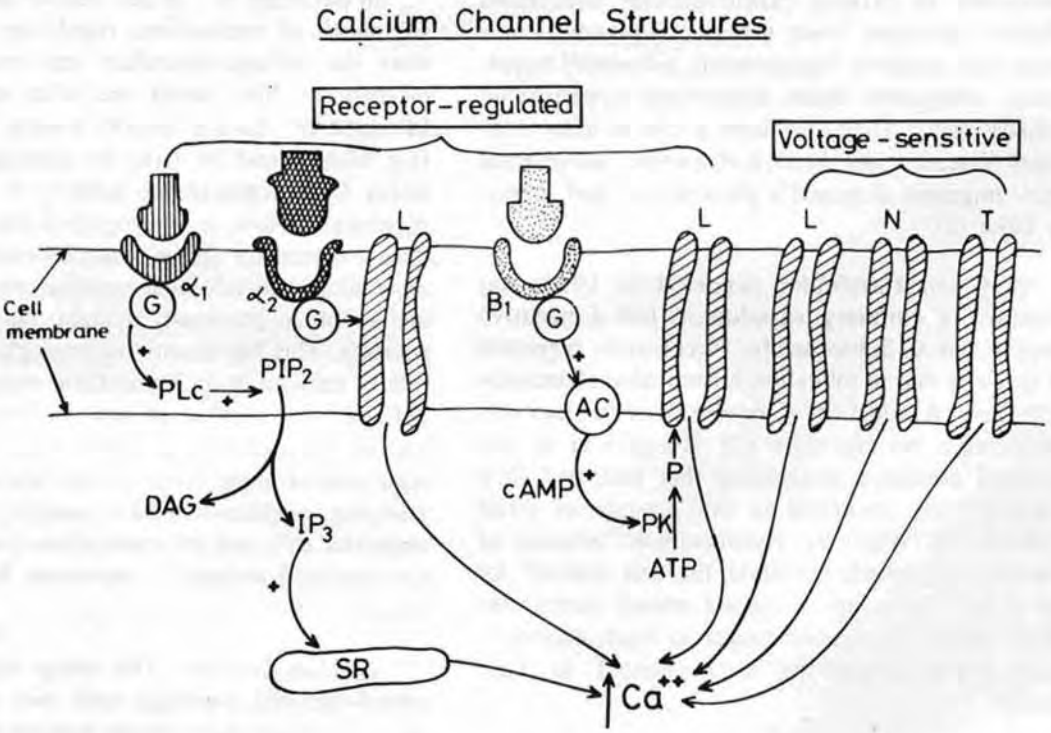

Fig. 1 : Diagrammatic representation of Calcium Channels. Ca^{++} — Intracellular Calcium, T- (Transient), N (Neuronal), and L (Long lasting) Voltage regulated Channels. AC-Adenyl Cyclase, G-G Protein, PK-Protein Kinase; P-Phosphorylation.
α_2 agonist, α_1 agonist, β_1 agonist
PL— Phospholipase C; PIP_2 —Phosphatidylinositol biphosphate; DAG —Diacylglycerol, PK_c —Protein Kinase; IP_3—Inositol triphosphate.

Intracellular calcium concentration increases by influx through membrane during activation of T, N or L voltage regulated channels. Receptor activation increases intracellular calcium by one of the following mechanisms depending upon the type of receptor stimulated. β_1-agonist binds with adenyl cyclase by G protein. The resulting increase in cyclic AMP activates a protein kinase to phosphorylate an L-channel, which facilitates intracellular calcium influx. Another agonist (α_1 receptor agonist) activates receptor linked by G-protein to channel through which calcium can enter cell. This is suggested to be the L channel regulated directly by α_2-receptor. The receptor regulated by α_1 agonist activates phospholipase C, resulting in breakdown of phosphatidylinositol biphosphate. This leads to the release of diacylglycerol, leading to activation of protein kinase C and inositol triphosphate which serves as intracellular second messenger. Binding of inositol triphosphate to receptors on sarcoplasmic reticulum leads to the release of calcium (modified from Zelis & Moore, Circulation, 1989; 80 suppl IV, IV-14-IV-16).

The voltage sensitive channels are further divided into subtypes L (long lasting or 'slow' channel), N (neuronal) and T (transient or 'fast') channels, based on their voltage sensitivity and conductance (5,6). The T and L channels are found in cardiac and vascular smooth muscles. These tissues are devoid of N channels which are seen only in nerves. Calcium conductance is low in the T channel, high in L channel and intermediate in the N channel (7). In neuronal tissue, the T channels are activated easily when the transmembrane potential becomes less negative than –70mV (8). The N and the L channels are more difficult to activate. Transmembrane voltage must be reduced by a greater extent, requiring a potential of about –10mV before activation occurs (8). The transient or T channels are rapidly inactivated, this is why calcium conductance is low. The long lasting or L channels are more slowly inactivated, thus allowing for a greater net conductance. The N channels are intermediate (7,8).

The three channels are specifically blocked by different agents. The T channels are resistant to blockade by most agents. Only nickel can inhibit calcium conductance. Both N and L channels can be blocked by cadmium and the venom of marine snail *Conus geographicus* (ω-conotoxin). It is only the L channel that is sensitive to blockade by the organic calcium antagonists such as diltiazem, verapamil and nifedipine.

In the neuronal tissues, both N and L channels exist. The organic calcium channel blockers can inhibit the calcium influx mediated by L channels but have very little effect on neurosecretory coupling (8,9), suggesting thereby that calcium influx can be compartmentalized within the cell.

Clusters of N channels have been found around areas of membrane fusion points where synaptic vesicles fuse with the membrane to release their contents into the neuroeffector junction. Further, ω-conotoxin inhibits L channels in neuronal tissues but not elsewhere (7). This suggests that there might be more than one species of L channels.

Receptor - regulated calcium channels: The mechanism by which intracellular concentration of calcium is increased is presented in Fig. 1. Three types of receptors are shown with three different types of agonists, coupled by a G-protein to a specific mechanism. The T and N regulated channels represent a pure voltage-sensitive mechanism to increase intracellular calcium concentration from an extracellular source, the receptor operated mechanism that works by causing intracellular calcium concentration to rise by release from intracellular storage sites. This is the mechanism when α_1-adrenergic receptors are stimulated.

α_1-receptor stimulation activates phospholipase C, which hydrolyses phosphatidylinositol biphosphate, cleaving it into two active components, diacylglycerol, which activates protein kinase C, and inositol triphosphate (IP_3). IP_3 serves as an intracellular messenger that interacts with receptors on the sarcoplasmic reticulum to cause calcium release from this intracellular organelle.

A receptor-operated mechanism that can modulate calcium influx by a voltage regulated channel is depicted in Fig. 1. Here a receptor agonist results in the phosphorylation of an L channel by a cyclic-AMP dependent protein kinase. In the phosphorylated state, the L channels are more likely to open in response to membrane depolarization and whole cell conductance increases. A prototype of this mechanism is that activated by the β_1-adrenergic agonist in the heart. In addition to the phosphorylation of the L-type voltage-sensitive channel, the protein kinase activated by cyclic AMP also phosphorylates a protein in the sarcoplasmic reticulum, which enhances calcium uptake by this organelle. The result of activating this mechanism is an intense calcium pulse of shorter duration.

The vascular smooth muscle does not contain an L channel that can be phosphorylated by a β-receptor mediated activation of adenylate cyclase. Rather in smooth muscle, β-receptor stimulation leads to activation of a cyclic AMP dependent protein kinase. In *in-vitro* systems, phosphorylation of myosin light-chain kinase renders it less sensitive to activation by the calcium-calmodulin complex - a mechanism proposed to explain vascular smooth muscle relaxation by β-receptor stimulation. However, recent evidence suggests that the myosin light-chain kinase phosphorylation sites required for enzyme desensitization are not

the sites that are phosphorylated *in-vivo*. The middle receptor seems to be directly coupled by a G protein to a calcium channel (7). With receptor activation, an influx of calcium occurs through this channel. The evidence that such a channel exists is based on the observation that certain receptor-operated mechanisms are very sensitive to inhibition by organic calcium channel blocking agents. The post junctional L-receptor in vascular smooth muscle would be a prototype of this mechanism (7). This might represent another species of L-type channel.

The evidence presented above suggests that a number of different L-type channels exist, all of which can be blocked by the organic CCB (9). In nerves, the L channels can also be blocked by ω-conotoxin. Some L-type channels, such as those in cardiac muscle, can be phosphorylated by a cyclic AMP dependent protein kinase, a process that facilitates calcium influx (7). In vascular smooth muscle, it is possible that L-type channels can be linked to α-adrenergic stimulation, and can increase calcium influx. In skeletal muscle, the T tubules are a rich source of dihydropyridine receptors, which bind to organic CCB with high affinity (10). Based on reconstitution studies, these dihydropyridine receptors closely resemble and might, infact, be a form of the L channel. These dihydropyridine receptors are clearly involved in excitation-contraction coupling. However, their exact function in excitation-contraction coupling is unclear. Many of the T tubular dihydropyridine receptors are found in close physical association with feet structures on the sarcoplasmic reticulum. These feet structures are thought to represent the sarcoplasmic reticular Ca^{2+} -release channel and the ryanodine receptor (11).

In skeletal muscle excitation-contraction coupling, whether these dihydropyridine receptors cause voltage-sensitive Ca^{2+} release by a direct conformational effect on the ryanodine receptor, is not yet settled.

In nerves, calcium influx through N-type channels causes neurosecretory coupling, whereas L channel activation (and inhibition) affects nerve function only under extreme conditions. Calcium influx through a cardiac L channel being phosphorylated by a cyclic AMP dependent kinase, can potentiate contractility in the heart by a calcium mechanism acting at the level of this filament. When the receptor stimulation in smooth muscle increases Ca^{2+} , the increase in vasomotor tone is caused by a myosin regulated mechanism. Thus, when sympathetic nerves are activated and the physiological neurotransmitter norepinephrine is released, all the stimulatory effects on the cardiovascular system are mediated by increasing intracellular calcium depending whether norepinephrine is interacting with a β_1-, α_2-, or α_1- adrenergic receptor.

Classification of CCB: Nayler et al (12) have divided CCB into 3 groups.

(a) *The organic blockers* including verapamil, gallopamil, nifedipine, niludipine, nimodipine, amlodipine, isradipine nicardipine, nitrendipine, diltiazem, prenylamine, fendiline.

(b) *Inorganic blockers* e.g. cations like La^{3+} , Mn^{2+}, Co^{2+} , Na^{+}.

(c) *Energy dependent blockers* e.g. cyanide, dinitrophenol.

The organic CCB include all the clinically relevant drugs and have been further subdivided by Fleckenstein (9) into :—

(i) *Highly potent & specific substances* like verapamil, diltiazem, nifedipine (and related dihydropyridines).

(ii) *Less specific substances* like prenylamine, fendiline, cinnarizine, perhexiline and caroverine.

(iii) *Non-specific agents* e.g. phenytoin, chlorpromazine, indomethacin and high doses of some beta blockers.

They can also be divided by their chemical structures into:

Gr. 1: *Dihydropyridine compounds* e.g. nifedipine, nimodipine, nisoldipine, niludipine, Py 108-068, nicardipine.

Gr. 2: *Benzothiazepin compounds* e.g. diltiazem.

Gr. 3: *Phenylalkylamines* e.g. verapamil, gallopamil, tiapamil.

Effects of Calcium Channel Blockers on Electrophysiological Activity of Heart

(I) *S-A node, A-V node and atria :* Calcium channel blockers cause reduction in the rate of sinus node discharge (negative chronotropic) and decrease in the velocity of conduction of electrical impulse through A-V node (negative dromotropic) (12). *In-vitro* and *in-vivo* effects of calcium channel blockers on these depressant effects differ considerably. In isolated preparation of atrial tissue, almost all calcium channel blockers have been shown to slow the rate of S-A node discharge and prolong the A-V conduction time, the latter being evident by a prolonged effective refractory period in the action potential. On the other hand, in conscious animals, an intact autonomic nervous system considerably modifies these electrophysiological effects of the calcium channel blockers. A significant reflex sympathetic action due to peripheral vasodilatation nullifies or even reverses the depressant action of nifedipine on the heart (13). This is not encountered with verapamil and diltiazem due to their nonspecific antagonism (14). Re-entrant A-V nodal tachycardia is prevented by verapamil which is due to its property of prolonging the A-V nodal refractoriness (15).

(II) *Effect on ventricular electrical activity:* Effects of calcium channel blockers on the electrophysiology of the ventricular tissue and ventricular arrhythmias have also been investigated. Verapamil suppresses the spontaneous and electrically activated rhythm of the Purkinje fibres while depressing the excitability (16). Automaticity of ventricular muscle fibre is markedly resistant to calcium channel blockers. Experimental ventricular arrhythmias caused by myocardial ischemia have been found to be responsive to calcium channel blockers (17).

(III) *Effect of Calcium Channel Blockers on triggered activity causing cardiac arrhythmias:* The precise electrophysiological mechanism of triggered activity at phase 4 of cardiac action potential giving rise to different types of cardiac arrhythmias, is not known.

However, oscillatory increase in the intracellular Ca^{2+} concentration has been found to play some role in their genesis (18). Verapamil and gallopamil have been found to prevent or correct such triggered activity (19).

Calcium Channel Blockers and Vascular Smooth Muscle: Chronic systemic hypertension is now generally considered to be caused by an increased peripheral vascular resistance, with cardiac output remaining unaltered (20). The etiology of this raised peripheral vascular resistance is multiple. Augmented sympathetic outflow has been found to play an important role in its pathogenesis. There is now ample evidence, based on information gathered from animal experiments, that several other factors can act independently or jointly to cause an increased sympathetic outflow. These are: (i) stress induced increased central sympathetic outflow (21), (ii) abnormally large release of norepinephrine (NE) from nerve endings (22), (iii) resetting of the baroreceptors which normally supervise the homeostatic control of blood pressure (23). Apart from NE, other circulating substances which can augment the vascular responsiveness are angiotensin II, 5-hydroxytryptamine (5-HT) (24) and an endogenous Na^+–K^+ ATPase inhibitor (natriuretic hormone) (25). All these factors cause an increased vascular resistance. Because the onset of hypertension is chronic and symptomless, by the time it is detected, the etiological factors can be dampened secondary to adaptations due to chronic rise of blood pressure.

Ca^{2+} and Vascular Smooth Muscle: Ca^{2+} constitutes the link between different factors causing augmented vascular responsiveness and vascular spasm. Actin and myosin interaction in smooth muscle cell depends on the phosphorylation of myosin light chain kinase, activated by calmodulin-Ca^{2+} complex (26,27).

Both voltage-operated and receptor-operated channels bring about an augmented influx of extracellular Ca^{2+}. In the voltage-dependent Ca^{2+} influx, depolarisation of the membrane plays an important role. 'Receptor-operated' influx of activator Ca^{2+} stimulated by some vasoconstrictor agents, e.g. norepinephrine, histamine, 5-HT etc., provides a bypass pathway that works unrelated to bioelectric membrane excitation (28).

The following sections deal with the effects of calcium channel blockers on two types of vessels,

(i) extramural coronary arteries and (ii) other systemic arteries.

Extramural coronary smooth muscle relaxation by Calcium Channel Blockers: The property of calcium channel blockers to dilate the coronary vessels and thus increase the coronary blood flow, is one of their most important circulatory effects. These drugs cause an interruption of transmembrane Ca^{2+} influx and thus block two processes, (a) the 'voltage-operated' transmembrane Ca^{2+} supply, thus inhibiting excitation-contraction directly and (b) the transmembrane refilling of intracellular Ca^{2+} pools. From these latter sites activator Ca^{2+} is released 'non-electrically' by vasoconstrictor substances, e.g., NE, histamine and 5-HT. These Ca^{2+} pools are mainly (i) superficial, loosely membrane bound Ca^{2+}, (ii) tightly membrane bound Ca^{2+}, (iii) Ca^{2+} stored in sarcoplasmic reticulum and (iv) Ca^{2+} stored in the internal surface of the membrane. It is presumed on the basis of some experimental data that in coronary smooth muscles the cellular Ca^{2+}-pools are less rich and require a regular and rapid transmembrane replenishment of Ca^{2+} than peripheral vascular smooth muscle. Thus, calcium channel blockers apart from blocking 'voltage-dependent' contractile activation of coronary smooth muscle, also diminish the Ca^{2+} replenishment needed for vasoconstrictor substance which induces phasic contractions.

Calcium Channel Blockers and peripheral vascular smooth muscle: Vascular smooth muscle relaxation by calcium channel blockers is quite indistinguishable from that of coronary smooth muscle, described in the previous section, i.e. direct relaxation by inhibition of transmembrane Ca^{2+} influx through 'voltage-dependent' channels or through some 'receptor-operated' channels and indirect relaxation by depletion of cellular Ca^{2+}-pools where contractile response is due partly to Ca^{2+}-releasing vasoconstrictor substances. But, unlike coronary smooth muscle cells, the cellular Ca^{2+}-pools are rather rich in Ca^{2+} and do not require a rapid replenishment by transmembrane Ca^{2+} influx. Several experimental observations have confirmed that calcium channel blockers prevent the increase in Ca^{2+} permeability of the membrane due to depolarisation, but is less effective in antagonising the release of activator Ca^{2+} from C^{2+}-pools by vasoconstrictor agents, e.g., norepinephrine (29,30).

TABLE I : Pharmacokinetics of the Calcium Channel Blockers.

Agents	Synonym	Absorption %	Bioavailability %	Protein binding %	Volume of distribution l/kg	$t_{1/2}$	Clearance ml/min/kg
Nifedipine 5, 10 mg Tab. capsule	Calcigard Depin, Nifelat Myogard, Nifedine	>90	65	95	1.32	~5	500-600
Nifedipine retard SR Tab.							500-600
Diltiazem (30, 60 mg Tab.)	Dilgina, Nengil	>90	35-60	78	5.0	4.1–5-6	15
Diltiazem SR (90, 120mg SR Tab.)	Diltime SR	> 90	35-60	78	5.0		15
Verapamil (40, 80, 120 mg Tab.) Inj. 5 mg/ml	Cordilex, Isoptin Vasopten, Veramil	> 90	10-20	90	4.3	6±4 (i.v.) 8±6 (p.o.)	13±7
Verapamil SR		> 90	10-20	90	4.3		13±7

Calcium channel blockers and stretch-induced autoregulatory vasoconstriction: Biedl and Reiner in 1900 (32) and Bayliss in 1902 (33) first postulated the phenomenon of vasoconstrictive autoregulation of blood supply. When the pressure within a blood vessel increases, the vascular wall tends to constrict to maintain a constant blood flow through an organ inspite of changes in arterial perfusion pressure. This phenomenon has been found to be present in renal, cerebral, coronary, intestinal and skeletal arteries (34). As vascular contractile responses require Ca^{2+}, this event is also responsive to the action of calcium channel blockers.

Apart from its physiological role, the auto-regulatory vasoconstriction might also play a significant role in the pathophysiology of essential systemic hypertension.

Ca^{2+} -regulated processes in non-cardiovascular tissues: Apart from cardiovascular system, Ca^{2+}-dependent smooth muscle contraction plays a key role in normal and pathological conditions of other organs in the body. These are listed below:

Ca^{2+} -regulated process	Physiological or pathological condition
1. Bronchial smooth muscle (35-38)	Bronchial tone or Bronchospasm.
2. Uterine Smooth muscle (39, 40)	Parturition, Dysmenorrhea.
3. Gastrointestinal smooth muscle (41)	G.I. Spasm, G.I. Motility, Esophageal spasm.
4. Genitourinary smooth muscle (42)	Ureteric spasm.

Ca^{2+} also plays a key role in the stimulation-secretion coupling phenomenon in non-motile cells. Exocytosis from these cells have been found to be initiated by an increased level of cytosolic Ca^{2+} concentration and to a considerable extent requires transmembrane Ca^{2+} influx through the calcium channel (43). So it is quite evident that as in the case of stimulation-contraction coupling, Ca^{2+} plays the role of the second messenger also in excitation-secretion coupling. Calmodulin, a cytosolic high-affinity calcium-binding protein, binds the cation and triggers the cellular event, as in the case of smooth muscle. Ca^{2+} induced release of lysosomal enzymes and Ca^{2+}-activated phospholipases leading to prostaglandin synthesis, are two other examples of calcium interactions in secretory cells.

The following table shows some organs where Ca^{2+} regulates the stimulation-secretion coupling process. So the ubiquitous role played by Ca^{2+} in activation of different excitable cells suggests the potential of calcium channel blockers in the treatment of some non-cardiovascular diseases as well.

Cells	Ca^{2+} -regulated process
1. Adrenal medulla	Stimulation of catecholamine release.
2. Juxtaglomerular apparatus	Inhibition of renin secretion.
3. Pancreas	Stimulation of glucose-induced insulin secretion.
4. Mast cells	Stimulation of histamine release.
5. Platelets	Stimulation of aggregation.

Pharmacokinetics: The absorption of CCB is nearly complete after oral administration. Bioavailability may be reduced because of first pass hepatic metabolism. First pass hepatic metabolism is extensive for verapamil and diltiazem. The effects of drugs are manifested within 30-60 min. of an oral dose. Peak effect of intravenous verapamil is evident within 15 minutes. Plasma protein binding is significant (70-99%). The elimination half-life is 1.5-5 hours. Nifedipine and verapamil are excreted primarily in the urine and diltiazem in the feces. Repeated oral administration may lead to an increase in bioavailability and half-life because of saturation of hepatic metabolism. In patients with hepatic cirrhosis, the bioavailability and half-lives of the CCB are increased (44,45) (Table-II).

TABLE II : Tissue selectivity of Calcium Antagonists.

Drug	Myocardial Contractility	Vasculature	Conducting and Nodal tissue
Verapamil	+++	+++	+++
Diltiazem	++	+++	++
Nifedipine	++	++++	+

orally in combination with digoxin in treating acute and chronic atrial fibrillation (77).

Atrial Flutter: Intravenous verapamil controls the ventricular response in atrial flutter by increasing the A-V block (77, 78). It may cause the development of atrial fibrillation with a controlled ventricular response (77).

Paroxysmal Supra-Ventricular Tachycardia (PSVT): Most cases of SVT are due to intranodal reentry or circus movements and two-thirds of ectopic atrial tachycardias convert to sinus rhythm with verapamil (77). Verapamil may be preferable over other agents especially if there is an urgent need to terminate the PSVT (action within 3 minutes) or in patients of coronary artery disease or peripheral vascular disease (77). It can also be used for prevention of PSVT (79).

Systemic Hypertension: CCB are effective as antihypertensive agents because of peripheral vasodilatation, antiadrenergic and natriuretic actions (80) and direct negative inotropic actions. CCB reduce both systolic and diastolic blood pressures with minimum side effects (81). They do not affect the blood pressure in normotensive persons (81). They may be most useful in patients with low renin hypertension (82). CCB have also been found to be beneficial in severe hypertension and hypertensive crises (81, 82) by the oral, sublingual or intravenous route (81).

Hypertrophic Cardiomyopathy (HCMP): The reasons for the beneficial effects of verapamil in HCMP are not clear. Verapamil reduces left ventricular outflow obstruction (83) but not as a result of reduction in left ventricular hypercontractility (84).

Improvement in diastolic function results in increased end-diastolic volume which decreases the venturi forces moving the mitral valve leaflet towards the septum (84). This in turn may decrease the obstruction and reduce myocardial stress (83) Verapamil has proved to be effective in patients refractory to propranolol (84).

Congestive Heart Failure: The clinical experience with CCB in heart failure is limited. Vasodilatation causes a reduction in after-load but the negative inotropic action of CCB counters their effect on the after load (85).

Hemodynamic studies have shown significant reductions in systemic vascular resistance along with the increase in cardiac output (86).

Patient with left ventricular dysfunction and normal levels of left ventricular after-load and those with outflow obstructions are more likely to have unfavorable effects (87). The present evidence suggests that CCB should be used in CHF only if additional indications exist e.g. angina or systemic hypertension.

Anti Atherogenic Properties: Studies in several types of animal models especially cholesterol fed rabbits, have shown that calcium antagonists can reduce the accumulation of atherogenic lesion components and decrease the progression of lesions. They may do this by a combination of decreasing calcium accumulation within arterial wall cells and by altering calcium channel independent metabolic activities, which affect the development of the lesion (88,89).

(B) *Non-Cardiac uses of CCB*

Neurological disorders: The use of CCB in neurological disorders has been limited because of their mild inhibition of the CNS Ca^{2+} channel activity. Nimodipine and flunarizine are the drugs which have been tried.

Migraine Prophylaxis: The effect of CCB in migraine prophylaxis is now well established. CCB prevent vasoconstriction by inhibition of Ca^{2+} influx via voltage and receptor channels. The onset of action is delayed, taking upto two weeks and it leads to a reduction in both the frequency and severity of attacks. Studies have shown that 80-90% of patients with vascular headaches benefit from nimodipine (90). While verapamil and nifedipine are also effective as prophylactic drugs, they have more systemic side effects being less selective for cephalic vessels (91). Some patients experience an initial exacerbation on first taking CCB and later find relief (92).

Sub Arachnoid Hemorrhage: Vasospasm following subarachnoid hemorrhage (SAH) is a major cause of morbidity due to the resulting cerebral ischemia. Vari-

ous studies involving nimodipine have been published showing its efficacy in reducing the severity of post SAH vasospasm and its resultant morbidity (93,94). Nimodipine reduces the frequency and severity of ischemic defects, penetrates the blood brain barrier effectively and has no significant side effects. The mechanism of action may be related to vasodilatation or to blocking a calcium ion dependent 'cascade' of biochemical processes leading to cell damage, preventing a calcium induced decrease in red blood cell deformity and improving cell energy production (95).

Cerebro Vascular Accidents (CVA): Both nimodipine and flunarizine have been shown to have some effect on the course of CVA (96).

Vertebro Basilar Insufficiency: Nimodipine and flunarizine reduce vertebrobasilar insufficiency though it is not clear whether this is the result of a direct vestibular action or via increased regional blood flow (96).

Vertigo: Deka (97) has reported beneficial effects of cinnarizine, a selective calcium channel antagonist in Meniere's disease, cervical spondylosis, sudden deafness and vestibular neuronitis.

Epilepsy: Flunarizine has been found to be useful in reducing seizure activity in experimental settings as well as in patients not responding to conventional therapy (96). Whether CCB can function as independent anti-epileptics is under investigation.

Psychiatric Disorders: CCB have been found to be useful in manic depressive psychosis, depression, schizophrenia and tardive dyskinesia. Verapamil, when used in mania, was found to have significant beneficial effects (98).

Pheochromocytoma: Symptomatic relief occured in a patient with a noradrenaline secreting pheochromocytoma while on nifedipine treatment. Studies suggest that nifedipine interferes with the myocardial action by acting directly on vascular smooth muscle (99).

Pulmonary Hypertension (PHT): The treatment of PHT continues to be unsatisfactory. The main focus of attention is on vasodilator drugs. Most drugs have been shown to have favorable acute benefits with reduced pulmonary vascular resistance and increased cardiac output but the increased stroke work of the right ventricle ultimately leads to worsening of right ventricular function. CCB given in high doses titrated to the hemodynamic response have caused dramatic reductions in pulmonary artery pressure and pulmonary vascular resistance along with regression of right ventricular hypertrophy. However, less than half of the patients respond to this regimen, especially ones with early and less advanced disease. Responses of the pulmonary vasculature to prostacycline may be predictive of response to CCB according to some preliminary studies (100,101).

Gastrointestinal Diseases

Achalasia: There are a number of reports suggesting the role of CCB especially nifedipine in the medical management of achalasia. The lower esophageal sphincter pressure is reported to decrease by as much as 50% without any significant side effects. This effect is believed to be due to the spasmolytic action of CCB on smooth muscle cells (102).

Diffuse Esophageal Spasm: Nifedipine is known to improve the symptoms related to diffuse esophageal spasm though at the cost of significant side effects (102).

Gynecological Disorders: Verapamil has been found to have relaxant effects on isolated human myometrium though *in-vivo* studies failed to reveal any action at tolerable therapeutic dosages.

Nifedipine has been shown to have a considerable inhibitory effect on uterine hypercontractility which is believed to be a major mechanism of pain in primary dysmenorrhea (99).

Oncology: The calcium channel antagonists verapamil, nifedipine, nitrendipine and caroverine have been found to increase the antineoplastic action of the drugs like vincristine, daunorubicin and adriamycin. It is mooted that they increase the cellular drug accumulation by blocking drug efflux (103).

Urinary Incontinence: Urinary incontinence due to detrusor instability can occur with damage to inhibitory neural pathways traveling along the lateral and ventral

ous studies involving nimodipine have been published showing its efficacy in reducing the severity of post SAH vasospasm and its resultant morbidity (93,94). Nimodipine reduces the frequency and severity of ischemic defects, penetrates the blood brain barrier effectively and has no significant side effects. The mechanism of action may be related to vasodilatation or to blocking a calcium ion dependent 'cascade' of biochemical processes leading to cell damage, preventing a calcium induced decrease in red blood cell deformity and improving cell energy production (95).

Cerebro Vascular Accidents (CVA): Both nimodipine and flunarizine have been shown to have some effect on the course of CVA (96).

Vertebro Basilar Insufficiency: Nimodipine and flunarizine reduce vertebrobasilar insufficiency though it is not clear whether this is the result of a direct vestibular action or via increased regional blood flow (96).

Vertigo: Deka (97) has reported beneficial effects of cinnarizine, a selective calcium channel antagonist in Meniere's disease, cervical spondylosis, sudden deafness and vestibular neuronitis.

Epilepsy: Flunarizine has been found to be useful in reducing seizure activity in experimental settings as well as in patients not responding to conventional therapy (96). Whether CCB can function as independent anti-epileptics is under investigation.

Psychiatric Disorders: CCB have been found to be useful in manic depressive psychosis, depression, schizophrenia and tardive dyskinesia. Verapamil, when used in mania, was found to have significant beneficial effects (98).

Pheochromocytoma: Symptomatic relief occured in a patient with a noradrenaline secreting pheochromocytoma while on nifedipine treatment. Studies suggest that nifedipine interferes with the myocardial action by acting directly on vascular smooth muscle (99).

Pulmonary Hypertension (PHT): The treatment of PHT continues to be unsatisfactory. The main focus of attention is on vasodilator drugs. Most drugs have been shown to have favorable acute benefits with reduced pulmonary vascular resistance and increased cardiac output but the increased stroke work of the right ventricle ultimately leads to worsening of right ventricular function. CCB given in high doses titrated to the hemodynamic response have caused dramatic reductions in pulmonary artery pressure and pulmonary vascular resistance along with regression of right ventricular hypertrophy. However, less than half of the patients respond to this regimen, especially ones with early and less advanced disease. Responses of the pulmonary vasculature to prostacycline may be predictive of response to CCB according to some preliminary studies (100,101).

Gastrointestinal Diseases

Achalasia: There are a number of reports suggesting the role of CCB especially nifedipine in the medical management of achalasia. The lower esophageal sphincter pressure is reported to decrease by as much as 50% without any significant side effects. This effect is believed to be due to the spasmolytic action of CCB on smooth muscle cells (102).

Diffuse Esophageal Spasm: Nifedipine is known to improve the symptoms related to diffuse esophageal spasm though at the cost of significant side effects (102).

Gynecological Disorders: Verapamil has been found to have relaxant effects on isolated human myometrium though *in-vivo* studies failed to reveal any action at tolerable therapeutic dosages.

Nifedipine has been shown to have a considerable inhibitory effect on uterine hypercontractility which is believed to be a major mechanism of pain in primary dysmenorrhea (99).

Oncology: The calcium channel antagonists verapamil, nifedipine, nitrendipine and caroverine have been found to increase the antineoplastic action of the drugs like vincristine, daunorubicin and adriamycin. It is mooted that they increase the cellular drug accumulation by blocking drug efflux (103).

Urinary Incontinence: Urinary incontinence due to detrusor instability can occur with damage to inhibitory neural pathways traveling along the lateral and ventral

reticulospinal tracks, resulting in unpredictable involuntary voiding. Nifedipine by reducing detrusor contractions can improve continence (104).

Asthma: CCB are an important contribution to the drugs available to treat heart disease in patients with associated reactive airway disease. CCB do not cause bronchoconstriction unlike drugs like propranolol. They also inhibit exercise or allergen induced bronchospasm. Clinical trials have not shown any effect on resting bronchial tone in asthmatics. They are useful therefore mainly in the management of heart disease in asthmatics even though they do not cause bronchodilatation (105).

Hiccups: Hiccups not responding to conventional therapy responded to nifedipine 20 mg TID in one patient (99).

Renal Transplant: Patients of renal transplant treated with diltiazem had improved graft function after 6 months as compared to controls. Increased levels of cyclosporin also allowed reduction of cyclosporin dosage (106).

Raynaud's Phenomenon: CCB have found a place in the management of Raynaud's phenomenon (107) because of their ability to cause smooth muscle relaxation. Nifedipine is the drug of choice showing a significant reduction in vasospastic attacks after therapy for three weeks. Verapamil has not been found to be effective. Diltiazem has also been used (30-90mg TID).

Malaria: Malarial parasites have an obligate calcium requirements for intracellular growth and erythrocyte invasion. Verapamil, its analog RO 11-2933 and desipramine cause a dose dependent increase in the accumulation of chloroquine in human and mouse hepatocytes, thus breaking chloroquine resistance (108).

Side Effects: The risk of side effects depends on the route of administration, underlying disease and doses used. The side effects occur mainly due to vasodilatation, negative inotropic action and conduction delay. Vasodilatation leads to sodium retention, edema, weight gain, reflex tachycardia with occasional worsening of angina, headache, flushing and vertigo.

Negative inotropic action and conduction blocks are of concern in coronary artery disease, cardiomegaly and intractable heart failure (44), (Table III).

TABLE III : Incidence of common side effects of Calcium Channel Blockers.

Side effect	Percent Incidence		
	Verapamil	Diltiazem	Nifedipine
Headache	8	2	6
Flushing	8	1	12
Nausea	1	3	4
Constipation	30	22	—
Bradycardia	2	1	—
Ankle edema	—	2	15
Tachycardia	—	—	15

Interactions: Digoxin doses need to be reduced because of an increase in plasma concentration of digoxin by as much as 75% when combined with verapamil.

Propranolol when given in combination with nifedipine blunts the reflex tachycardia due to vasodilatation (45). Other interactions also occur and are given in Table IV.

TABLE IV: Drug Interactions with Calcium Channel Blockers.

Digoxin	Increase digoxin levels particularly with verapamil fall with nifedipine
Alpha-blockers	Additive/synergic effect on blood pressure
Beta-blockers	Reduce reflex tachycardia of nifedipine (caution with i.v. verapamil)
Antiarrhythmias	Avoid combination
H_2- antagonists	Increase calcium channel blocker level
Drugs increasing hepatic microsomal oxidase activity	Reduce CCB level
Anesthetics	Hypotension, tachycardia

Conclusion: Calcium channel blockers represent an important breakthrough in the history of medical therapeutics. With the ever increasing role of CCB in both cardiac and non cardiac conditions, and with the availability of more selective agents their potential is endless.

REFERENCES

1. Schwartz ML, Rotmensch HH, Frishman WH, et al. Potential application of calcium channel antagonists in the management of non cardiac disorders. In: Packer M, Frishman WH, eds. Calcium channel Antagonists in Cardiovascular disease. Norwalk Appleton-Century-Crofts, 1984; 371.
2. Fleckenstein JA, Kammermeier H, Doring H, Freund HJ. Zum Wirkungs — Mechanismus neurartiger koronardilatoren mit gfeichzeitig Sauerstoff-eins parenden myokard-Effekten, Penylamin and imroveratril. *Z Kreislaufforsch* 1967; 56: 716-744, 839-853.
3. Rougier O, Vossort G, Garnier D, et al. Existence and role of a slow inward current during the trans atrial action potential. *Pflugers Arch* 1969; 308: 91-110.
4. Caterall WA. Structure and function of voltage sensitive ion channels. *Science* 1988; 842: 50-61.
5. Zelis R, Wichmann T, Starke K: Inhibition by diltiazem of norepinephrine release from sympathetic nerves in the rabbit pulmonary artery. *Pharmacology* 1985; 31: 268-277.
6. Exton JH Mechanisms of action of calcium-mobilizing agonists: Some variations on a young theme. *FASEB J* 1988; 2: 2670-2676.
7. Hofmann F, Nastainczyk W, Rohrakasten A, Schneider T, Sieber M: Regulation of the L-type calcium channel. *Trends Pharmacol Sci* 1987; 8: 393-398.
9. Meldolesi J, Pozzan T: Pathways of Ca^{2+} influx at the plasma membrane: Voltage, receptor, and second messenger-operated channels. *Exp Cell* 1987; 171-283.
10. Rios E, Pizzaro G: Voltage sensors and calcium channels of excitation-contraction coupling. *NIPS* 1988; 3: 223-227.
11. Hymel L, Fleischer S, Schindler H: Purified ryanodine receptor of skeletal muscle sarcoplasmic reticulum forms Ca^{2+} -activated oligometric Ca^{2+} channels in plannar bilayers. *Proc Natl Acad Sci USA* 1988; 85: 441-445.
12. Zipes DP, Fischer JC. Effects of agents which inhibit the slow channel on sinus node automaticity and atrioventricular conduction in the dog. *Circ Res* 1974; 34: 184-192.
13. Ellrodt G, Chew CYC, Singh BN. Therapeutic implications of slow channel blockade in cardiocirculatory disorders. *Circulation* 1980; 62: 669-679.
14. Singh N, Nademanee K, Baby SH. Calcium antagonists: Clinical use in the treatment of arrhythmias. *Drugs* 1983; 25: 125-153.
15. Wit AL, Cranefield PF. Effect of verapamil on the sinoatrial and atrioventricular nodal tachycardia. *Circ Res* 1974; 35: 413-425.
16. Kaumann AJ, Serut JR. Optical isomers of verapamil on canine heart. Prevention of ventricular fibrillation by coronary artery occlusion impaired atrioventricular conductions and negative inotropic and chronotropic effects. *Naunyn Schmiedebergs Arch Pharmacol* 1975; 291: 347-358.
17. EL-Sherif N, Lazzara R. Re-entrant ventricular arrhythmias in the late myocardial infarction period. Effect of verapamil and D-600 and the role of the 'slow channel'. *Circulation* 1979; 60: 605-615.
18. Kass RS, Lederer WJ, Tslen N. Role of calcium ions in transient inward currents and after contractions induced by-strophanthidin in cardiac Purkinje fibres. *Physiol (London)* 1978; 271: 187-208.
19. Cranfield PF. Action potentials, afterpotentials, and arrhythmias. *Circ Res* 1977; 41: 415-423.
20. Hulthen UL, Bolli P, Amann FW et al. Enhanced vasodilatation in essential hypertension by calcium channel blockade with verapamil. *Hypertension* 1982; 4: (Suppl II), II-26 II-31.
21. Brody MJ, Bron KW, Faber JE, Hartte DK, Lappe RW. In: Sleight P, Freis ED, eds. Cardiology, Vol I, Hypertension London, Butterworths, 1982; 199-221.
22. Vanhoutte PM, Webb RC, Collis MG. Pre- and post junctional adrenergic mechanisms and hypertension. *Clin Sci* 1980; 59 (Suppl 6): 2115-2238.
23. Mark AL, Mancia G. In: Shepherd JT, Abbound FM. eds. Handbook of Physiology, Section 2. The cardiovascular system. Bethes etc. *American Physiological Society* 1983; 795-812.
24. Van Nueten JM. 5-HT and precapillary vessels. *Fed Procs* 1983; 42: 223-227.
25. Vanhoutte PM, Lorenz RR. Na^+ K^+ —ATPase inhibitions and the adrenergic neuro effector interactions in the blood vessel wall. *J Cardiovasc Pharmacol* 1984; 6: 588-594.
26. Stolet JC, Hugniterc, Illien B, Landry M. In: Vanhoutte PM, Leusen I. eds. Vasodilatation. New York, Raven Press, 1981; 355-371.
27. Murphy RA, Certhoper WT, Treventhick MA, Singer HA. Calcium dependent regulatory mechanisms in smooth muscle. In: Vanhoutte PM, Vatuer SF. eds. Vasodilator mechanisms. Basel, S. Karger, 1984; 229-242.
28. Fleckenstein A. Calcium Antagonism in Heart and Smooth Muscle. New York, John Wiley and Sons, 1983; 244-259.

29. Heausler G. Differential effect of verapamil on excitation contraction coupling in smooth muscle and on excitation secretion coupling in adrenergic nerve terminals. *J Pharmacol Ther* 1972; 180: 672-682.

30. Bilek I, Peiper U. The influence of verapamil on the noradrenaline activation of the isolated aorta and portal vein of the rat. *Pfligers Arch ges Physiol* 1973; 342 (Suppl): R57.

31. Bilek I, Laven R, Peiper U, Regnat K. The effect of verapamil on the response to noradrenaline or to potassium depolarization in isolated vascular strips. *Microvasc Res* 1974; 7: 181-189.

32. Beidl A, Runer M. Studien Uber Himirculation and Himodem, II. Zur Froge der Innervation der Himgefasse. *Pfligers Arch ges Physiol* 1900; 79: 158-194.

33. Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. *J Physiol (London)* 1902; 28: 220-231.

34. Folkow B. Description of the myogenic hypothesis, *Circ Res* 1964; 15 & 14 (Suppl I): 279-287.

35. Russi FW, Marchette B, Verger LS, Abraham WM, Ahmed T. Modification of allergic bronchoconstriction by a calcium antagonist-mode of action. *Am Rev Respir Dis* 1983; 127: 675-679.

36. Cerrina J, Denjean A, Alexandre G, Lokchart A, Duroux P. Inhibition of exercise-induced asthma by a calcium antagonist, nifedipine. *Am Rev Respir Dis* 1981; 123: 156—160.

37. Raemesh kD, Sommer J. Pharmacokinetics and metabolism of nifedipine. *Hypertension* 1983; 5 (Suppl II) : 8-24.

38. Tinkleman DG. Calcium channel blocking agents in the prophylaxis of bronchial asthama. *Am J Med* 1985; 78: 35-38.

39. Anderson KE. Effect of Calcium antagonists on uterine contractility. *Acta-Obstet Gynecol Scand* 1982; 108 (Suppl): 17.

40. Trimarco B, Deluca N, Ricciardelli B, Volpe M, Venicro A, Cuocolo A, Cucala M. Diltiazem in the treatment of mild to moderate hypertension. Comparison with metoprolol in a cross over double-blind trial. *J Clin Pharmacol* 1984; 24: 218-227.

41. Reynolds IJ, Gould RJ, Snyder SH. Loperamide: blockade of calcium channels as a mechanism for antidiarrhoeal effects. *J Pharmacol Exp Ther* 1984; 231: 620-632.

42. Forman AS, Andersson KE, Henriksen L, Rud T, Ulmsten U. Effects of nifedipine on the smooth muscle of the human urinary tract in vitro and *in vivo*. *Acta Pharmacol Toxicol (Copenh)* 1978; 43: 111-118.

43. Ross SD, Cardenas HL. Nerve Cell calcium as a messenger for opiate and endorphin actionsl. *Adv Biochem Psychopharmacol* 1979; 20: 301-306.

44. Seth SD, Maulik SK, Gupta YK. Calcium and calcium channel blockers. Experimental and clinical aspects. *Indian J Exp Biol* 1987; 25: 729-741.

45. Seth SD, Maulik SK, Gupta YK. Calcium channel blockers: an overview. In: Seth SD, Manchanda SC and Siddiqui HH. Calcium Channel Blockers and the Heart, eds. New Delhi Interprint India, 1989; 1-22.

46. Waters DD, Theraus P, Sclacheic J, et al. Provocative testing with ergonovine to assess the efficacy of treatment with nifedipine, diltiazem and verapamil in variant angina. *Am J Cardiol* 1981;. 48: 123-130.

47. Antman E, Muller J, Goldberg S et al. Nifedipine therapy for coronary artery spasm. *N Engl J Med* 1980; 302: 1269-1273.

48. Severi S, Davies G, Maseri A, et al. Long term prognosis of 'variant' angina with medical treatment. *Am J Cardiol* 1980; 46: 223-232.

49. Kimura E, Kishida H. Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan. *Circulation* 1981; 63: 844-848.

50. Liversley B, Carteley PF, Champbell RC et al. Double-blind evaluation of verapamil, propranolol and isosorbide dinitrate against placebo in the treatment of angina pectoris. *Br Med J* 1973; 1: 375-379.

51. Frishman WH, Klein NA, Strom JA et al. Superiority of verapamil to propranolol in stable angina pectoris-A double-blind randomized crossover trial. *Circulation* 1982; 65: (Suppl 1) 51-59.

52. Meuller HS, Chahine RA. Interim report of multicenter double blind placebo controlled studies of nifedipine in chronic stable angina. *Am J Med* 1981; 71: 645-657.

53. FrishmanWH, Charlap S, Kimmel B et al. Diltiazem compared to nifedipine and combination treatment in patients with stable angina: Effects on angina, exercise tolerance and the ambulatory ECG. *Circulation* 1988; 77: 774-786.

55. Weiner DA, Cutler SS, Klein MD. Efficacy and safety of sustained-release diltiazem in stable angina pectoris. *Am J Cardiol* 1986; 57: 6-16.

56. Bala Subramanian V, Parmasivan R, Lahiri A et al. Verapamil in chronic stable angina-A controlled study with computerized multistage treadmill exercise. *Lancet* 1980; i: 841.

57. Weiner DA, Klein MD, Cutler SS. Evaluation of sustained release verapamil in chronic stable angina pectoris. *Am J Cardiol* 1987; 59: 215.

58. Weiner DA. Calcium channel blockers. *Med Clin North Am* 1988; 72:83.

59. Pepine CG, Feldmann RL, Hill JA, et al. Clinical outcome after treatment of rest angina with calcium blockers, comparative experience during the initial year of therapy with diltiazem, nifedipine and verapamil. *Am Heart J* 1983; 106: 1341.

60. Beller GA. Calcium antagonists in the treatment of Prinzmetal's Angina and unstable Angina Pectoris. *Circulation* 1989; 80 (Suppl IV) : IV-78.

61. Frishman WH, Teicher M. Antianginal drug therapy for silent myocardial ischemia. *Am Heart J* 1987; 114: 140.

62. Frishman WH, Charlap S, Kimmel B, et al. Diltiazem compared to nifedipine and combination treatment. in patients with stable angina: Effects on angina, exercise tolerance and the ambulatory ECG. *Circulation* 1988; 77:774.

63. Epstein SE, Quyyumi AA, Bonow RO. Myocardial ischemia-silent or symptomatic. *N Engl J Med* 1988; 318:1038.

64. Millard RW, Lathrop DA, Crupp G. et al. Differential cardiovascular effects of calcium channel blocking agents: Potential mechanisms. *Am J Cardiol* 1982; 49: 499-506.

65. Ganguly PK, Srivastava LM, Seth SD et al. Nifedipine- a new calcium antagonist in experimental myocardial necrosis. *Indian J Med Res* 1981; 73: 617.

66. Ganguly PK, Bora PS, Seth SD et al. Alterations in isoproterenol induced cardiac metabolic changes by a calcium antagonist nifedipine. *Current Therap Res* 198; 31: 56-66.

67. Gupta MP, Seth SD, Manchanda SC, Singh Uma. Effect of nifedipine and hyaluronidase alone and in combination in myocardial preservation in experimental myocardial infarction-morphological and biochemical profile. In : Dhalla NS, Innes IR and Beamesh ERE, eds. Myocardial Ischemiatrans. Boston, Martinus Najhoff Publishing, 311-321.

68. Seth SD, Maulik SK. Calcium channel blockers in experimental myocardial infarction. In: Anand IS, Wahi PL, Dhalla NS. eds. Pathophysiology and pharmacology of heart diseases. New Delhi. Kluwer Academic Publishers 1989; 109-123.

69. Nayler WG. Cardioprotective effects of calcium ion antagonists in myocardial ischemia. *Clin Invest Med* 1980; 3: 91-98.

70. Yusuf S, Furberg C. Effect of acute or chronic antagonists administration of calcium antagonists on mortality following myocardial infarction. *J Am Coll Cardiol* 1987; 9:25A.

71. Wilcox RG, Hampton JR, Banks DC, et al. Trial of early nifedipine in acute mycardial infarction. The TRENT study. *Br Med J* 1986; 293: 1204-1212.

72. The Danish Study Group on Verapamil in Myocardial Infarction. Verapamil in acute myocardial infarction. *Eur Heart J* 1984; 5: 516, 106:341-347.

73. Gibson RS, Boden WE, Theoux P, et al. Diltiazem and reinfarction in patients with non Q-wave myocardial infarction. *N Engl J Med* 1984; 315-423.

74. Neufeld HN. Calcium antagonists in secondary prevention after acute myocardial infarction: The Secondary Prevention Reinfarction Nifedipine Trial (SPRINT). *Eur Heart J* 1986; 7 (Suppl B) : 51-64.

75. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; 319: 385-392.

76. Yusuf S, Furberg CD. Effects of calcium channel blockers on survival after myocardial infarction. *Cardiovasc Drug Ther* 1987; 1: 1343-1344.

77. Frishman WH, Lejemtel T. Electropharmacology of calcium channel antagonists in cardiac arrhythmias. *PACE* 1982; 5: 402-419.

78. Weiner I. Verapamil therapy for atrial flutter and fibrillation. In: Packer M, Frishman WH. eds, Calcium Channel Antagonists in Cardiovascular Disease. Norwalk Appleton-Century Crofts, 1984; 257.

79. Maukritson Dr. Winniford MD, Walker WS et al. Oral verapamil for paroxysmal supraventricular tachycardia:. A long-term double-blind, randomized trial. *Ann Intern Med* 1982; 96: 409-415.

80. Buhler F, DeLecuw PW, Doyle A, et al. Calcium metaolism and calcium-channel blockers for understanding and treating hypertension. *Am J Med* 1984; 177: 1-15.

81. Spivack C, Ocken S Frishman WH. Calcium antagnists: Clinical use in treatment of systemic hypertension. *Drugs* 1983; 25: 154-176.

82. Erne P, Bolli P, Bertel 0 et al. Factors influencing the hypotensive effects of calcium antagonists. *Hypertension* 1983; 5 (Suppl II): II-97-II-102.

83. Toresch M, Hirzel HO, JHenni R et al. Reduction of septal thickness following verapamil in patients with asymmetric septal hypertrophy. *Circulation* 1979; 59 (Suppl II): 11-155.

84. Rosing DR, Bonow RO, Packer M, et al. Verapamil therapy for the management of hypertrophic cardio myopathy. In Packer M, Frishman WH, eds. Calcium Channel Antagonists in Cardiovascular Disease. Norwalk Appleton-Century-Crofts, 1984; 31-46.

85. Henry PD, Borda L, Schuchleib R. Chronotropic and inotropic effects of vasodialators. In : Lichtlen PR, Kimura E, Taira N eds. International Adalat Panel Discussion: New Experimental and Clinical Results. *Excerpta Medica, (Amsterdam)* 1979; 14-22.

86. Singh BN, Ellrodt G, Nademance K. Calcium antagonists: Cardiocirculatory effects and therapeutic actions. In : Hurst JW (ed) : Clinical Essays on the Heart, New York, McGraw-Hill; 1984, p 65.

87. Charlap S, Frishman WH. Nifedipine for the treatment of congestive heart failure. *Int J Cardiol* 1984; 6: 665-672.

88. Weinstein DB, Heider JG. Anti-atherogenic properties of Calium antagonists. *Am J Med* 1986; (Suppl 4A): 27-32.

89. Buhler FR, Leren P, Lichtlen PR, et al. Anti-atherogenic potntial of calcium antagonists. *Atherosclerosis Reviews* 1990; 21: 201-206.

90. Meyer JS Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headache : *Headache* 1983; 26: 266-268.

91. Meyer JS, Doiwell R, Mathew NJ, et al. Clinical and hemodynamic effects during treatment of vascular headaches with verapamil. *Headache* 1984; 24: 313-315.

92. Martin JB. Headache. In: Wilson et al., eds. Harrison's Principles of Internal Medicine, 12th edition. New York, Mc Graw Hill Inc, 1990; 108.

93. Gelmer HJ, Gorter K, et al. A controlled trial of nimodipine in acute ischaemic stroke. *N Engl J Med* 1988; 318: 203-208.

94. Stean PA, Gisvold dSE, et al. Nimodipine improves outcome when given after complete cerebral ischaemia in primates. *Anesthesiology* 1985; 62: 406-412.

95. Applegate CN, Fox PT. Cerebrovascular disease. Dunagan WC, Ridney ML eds. In : Manual of Medical Therapeutics. Boston, Little Brown and Company, 1989.

96. Van Zwieten PA. The use of calcium entry blockers in the treatment of neurological disorders. *Prog Clin Neurosc* 1986; 2: 33-40.

97. Deka RC. Vertigo of cardiovascular origin. Calcium channel blockers in its management. In: Seth SD, et al. eds. Calcium channel blockers and the heart. New Delhi, Interprint, 1989; 161-163.

98. Martindale. The extra pharmacopoeia. Reynolds JEF, et al, eds. London, The Pharmaceutical Press 1989; 92.

99. Martindale. The extra Pharmacopoeia. Reynolds JEF et al, eds. London. The Pharmaceutical Press, 1989; 1513.

100. Rich S. High dose calcium blocking therepy for primary pulmonary hypertension: Evidence for long term reduction in pulmonary artery pressure and regression of right ventricular hypertrophy. *Circulation* 1987; 76: 135-142.

101. Rubin LJ. Prostacyclin induced pulmonary vasodilatation in primary pulmonary hypertension. *Circulation* 1982; 66: 334-339.

102. Schwartz ML, Rotmensch HH, Frishman WH, et al. Potential applications of calcium-channel antagonists in the management of noncardiac disorders. In: Packer M, Frishman WH, eds. Calcium Channel Antagonists in Cardiovascular Disease. Nowalk, Appleton-Century-Crofts. 1984; 371-394.

103. Cadan EC, Durivage HJ. Cancer Chemotherapy. In: Wilson et al, eds. Harrison's Principles of Internal Medicine. New York, Mc Graw Hill Inc, 1990.

104. Williams ME, Pannel FC. Urinary incontinence in the elderly. *Ann Intern Med* 1982; 97: 895-899.

105. Martindale. The Extra Pharmacopoeia. Reynolds JEF, et al eds. London. The Pharmaceutical Press; 1989; 1510.

106. Martindale. The Extra Pharmacopoeia. Reynolds JEF, et al eds. London. The Pharmaceutical Press 1989; 1947.

107. Scibold JR. Scleroderma (systemic sclerosis), In: Kelly WN et al., eds. Textbook of Rheumatology. Eds Kelly WN, et al. 3rd edition, Philadelphia, Saunders, 1989; 1215-1244.

108. Watt G, Long GW, Grogl M, et al. Reversal of drug resistant falciparum malaria by calcium antagonists: potential for host cell toxicity. *Trans R Soc Trop Med Hyg* 1990; 84: 187-190.