C A L C I U M A N T A G O N I S T S I N H Y P E R T E N S I O N

PHYSIOLOGICAL CONCEPTS AND THERAPEUTIC USE

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Calcium Antagonists in Hypertension

Index to Contents

Calcium antagonists have recently emerged as an important class of drugs useful in the treatment of cardiovascular disorders. These drugs not only signify a major advance in modern drug therapy but their actions have aided our understanding of the genesis of certain cardiovascular diseases. Few classes of pharmacologic agents have generated as much therapeutic interest as have calcium entry blockers during the last decade. A variety of terms have been used to describe this heterogenous group of compounds - calcium entry blockers, calcium antagonists, calcium influx blockers, slow channel blockers, calcium blockers, etc.. The term "calcium blockers" should probably be abandoned because blockade of calcium would be incompatible with life. For today's discussion, I will use the term "calcium antagonists" which is being increasingly utilized to describe the cellular mechanism of action of these compounds particularly with reference to the vascular smooth muscle physiology, and pathophysiology.

What Constitutes a Calcium Antagonist?

Fleckenstein introduced the term "calcium antagonists" in 1969 to describe the actions of compounds that mimicked the consequences of calcium withdrawal from physiological media (Fleckenstein et al 1969). The role of calcium in sustaining myocardial contractility was first recognized by Sidney Ringer more than a century ago (Ringer 1882). He observed that calcium free saline leads to cardiac arrest of the isolated frog hearts. Considerable evidence has accumulated in the last 20 years to confirm that calcium ions are a prerequisite for the activation of the principal enzyme in contractile energy expenditure, i.e. myofibrillar ATPase. Excitation of the myocardial sarcolemma membrane produces an immediate influx of calcium ions into the intracellular compartment and this influx may further trigger release of calcium ions from the intracellular sites. Thus calcium ions act as mediators in the excitation - contraction coupling between the sodium dependent electrical events on the cell surface and the calcium dependent intracellular processes that are transformed into mechanical events. The contractility is lost (reversibly) upon withdrawal of extracellular calcium. The crucial cell membrance components are the "channels" that permit or defy the permeability to various ions. Calcium because of its distinguished properties is the most important ion biologically and the function of this cation is underscored by the fact that no other electrolyte is under more vigorous control in the body than calcium. Under proper circumstances calcium antagonists are substances that (1) diminish contractile force (2) reduce the utilization of high-energy-phosphate compounds by the contractile system (3) lower the extra O_2 consumption during contractile activity and (4) lose their potency after the addition of Ca^{2+}.

Although the concept of Ca^{2+} antagonism with respect to drug action is relatively new, it is interesting to note that Tashinone, the active component of a traditional chinese remedy used for centuries for the treatment of cardiac disorders resembles calcium antagonists in its action (Patmore and Whiting, 1982).

The Ca^{2+} Current in the Smooth Muscle

The role of ionic fluxes in initiating excitation-contraction is well documentated in cardiac muscle (New and Trautwein, 1972; Corabouef 1978;

Reuter 1979) and a similar physiological event occurs in the vascular smooth muscle. In cardiac muscle excitation involves the activation of two distinct inward currents (Figure 1). The first of these inward currents is carried by Na+ and is seen as the fast upstroke of the action potential. The second current is carried mainly (not exclusively) by calcium (Beeler and Reuter 1970, Reuter 1979, Kass and Tsien 1975). The rapid upstroke (action potential spike) during phase 0 is caused by voltage dependent increase in sodium conductance; the thresold for activation of the fast (sodium) channel is between -60 and -70 mV. The slow inward current mediated by calcium is responsible for excitation-contraction coupling and the plateau phase of the action potential (Weidmann 1974). The kinetics of activation of the slow inward current are of slower magnitude than those of the fast channel (Reuter, 1973; Beeler and Reuter 1977); it reaches its peak when membrane potential is in the range of -20 to 0 mV. Although the slow channel is often referred to as the calcium channel, it must be remembered that to some degree sodium also enters through this channel (Goldman and Morad, 1977). The relative contribution of sodium to the slow inward current is complex and not fully understood. The slow channel, however, is 100 times more permeable to calcium than for sodium justifying the term "calcium channel." The so-called calcium channels have not yet been identified as distinct anatomic structures and could be considered as specific protein macromolecular structures. Each slow channel allows about 30,000 calcium ions to enter per second and there may be 30 channels per square micron of cell surface (Reuter 1974).

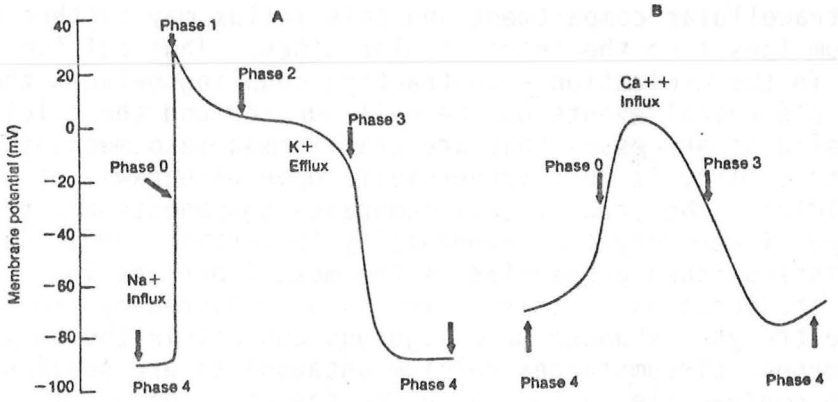


Figure 1: The action potential on the left is mediated by rapid influx of sodium ions. Action potential on the right is a "slow" response mediated by inward movement of calcium ions

The calcium channels can be envisaged as porous structures with each pore having its own set of 'activation' and 'inactivation' gates. In the resting state, the cytoplasmic free calcium concentration is not more than 10^{-7} M, so that the ratio of extracellular to intracellular Ca^{2+} exceeds 10^4. The calcium electrochemical gradient therefore is directed inward which means that calcium enters the cell freely when activated (Figure 2). The low intracellular calcium is due to a low permeability for calcium of the polarized plasma membrane and to several intracellular buffering processes. It is of note that even though cytoplasmic calcium constitutes a minute fraction of the total calcium pool, it represents an important variable in the regulation of cellular function. Two types of calcium

channels may be distinguished - the channels responsive to adrenergic stimuli have been termed "receptor operated" channels whereas those not affected by adrenergic modulation are termed as "voltage dependent" or "potential dependent" channels (Morad and Maylie 1980, Towart and Schramm 1984, Triggle 1981). Little is known of receptor operated channels; potential operated channels are activated by membrane depolarization (Triggle and Swamy 1983). Since these channels appear to be highly specific for a given ion, it is believed that the aqueous pore is endowed with selectivity that determines the type of ions that can traverse the channel. When the depolarization wave approaches the calcium channel, reduction of membrane potential causes the gate to open causing the influx of calcium. The gate closes when the resting transmembrane level is restored. Thus the calcium induced pathway of cellular activity depends not only on its availability but also by its regulation by the "channels" (Figure 3). Exposure of smooth muscle cells to an agonist not only enhances membrane permeability for Ca++ but also induces the release of Ca++ from intracellular stores. This latter phenomemon is responsible for transient contraction which can be induced in Ca++ free medium.

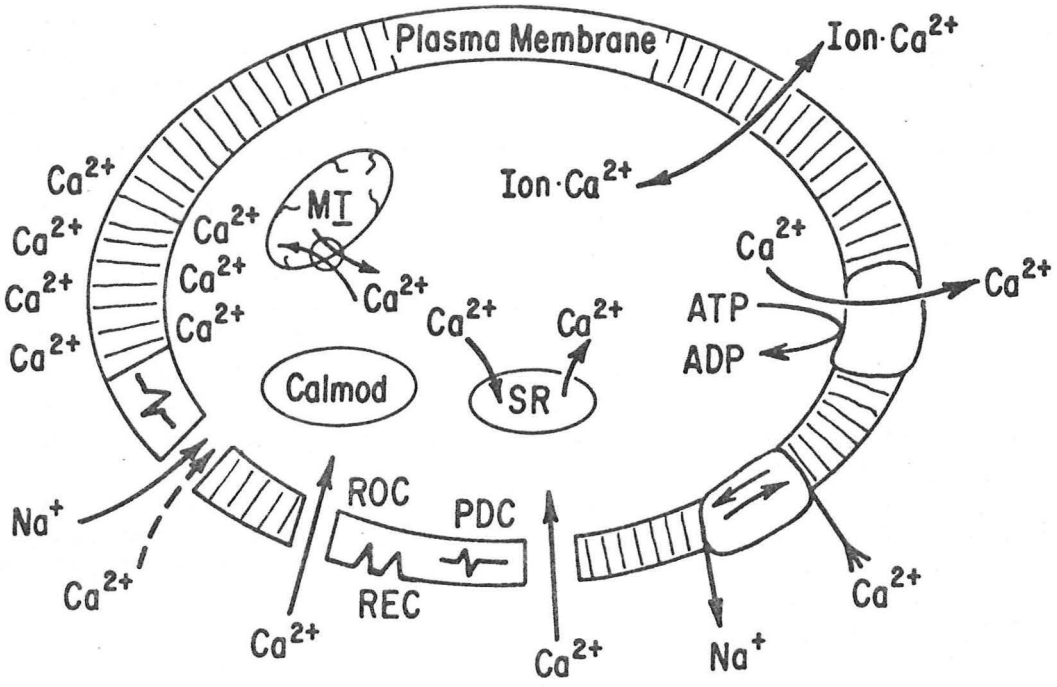


Figure 2: Representation of processes controlling cellular calcium movements. Calcium influx can occur through ion channels, including the fast sodium channel (a minor component) and through the potential dependent (PDC) and receptor operated (ROC) calcium channels. Additionally, calcium influx can occur as one component of a plasmalemmal sodium-calcium exchange process that can operate in either direction. Calcium pumping is represented by a plasmalemmal calcium-ATPase, but calcium sequestration (and release) can take place at several intracellular sites, including mitochondira (MI), sarcoplasmic reticulum (SR), and the internal surface of the plasma membrane. A nonphysiologic calcium entry process is represented by ionophore transport (Ion-Ca^{2+}). (Calmod-Calmodulin). From Triggle DJ, 1984.

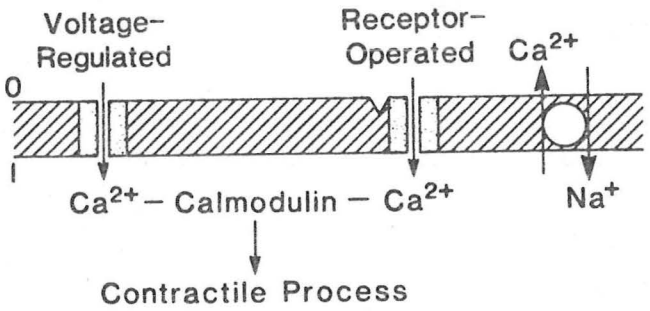


Figure 3: Diagram of membrane processes in smooth muscle cells. Calcium (Ca^{2+}) moves from outside (0) to inside (1) a cell through at least two types of channels, and is removed from the cell by a Na^{+}-Ca^{2+} exchange mechanism. Intracellular interaction of calcium with calmodulin leads to actin-myosin interaction. From Cohn JN 1983.

To maintain a steady intracellular concentration of calcium, there must be some mechanism(s) for the extrusion of Ca++ from the cell; otherwise calcium overload would occur resulting in cellular death. The calcium efflux is accomplished largely through active transport across the cell membrane. The two major calcium efflux systems are Na+/Ca++ exchange and the ATP dependent active calcium transport mediated by a Ca++ATPase regulated by calmodulin (Van Breemen et al 1979, Lang and Blaustein 1980, Casteels 1980, Mueller and Van Breemen 1979). The relative contribution of these mechanisms to the extrusion of calcium is not firmly established. However, it is unlikely that moment to moment calcium balance is achieved solely by the extrusion mechanisms as vascular relaxation can occur even when calcium efflux is inhibited (Somlyo and Somlyo 1983). Cellular concentration of calcium is also governed by its uptake by sarcoplasmic reticulum and mitochondria - the "cellular sinks" for calcium (Salaro 1982). Upon stimulation by an agonist, calcium stores released from within these intracellular depots (cytoplasm and sarcoplasmic reticulum) may contribute to the physiological contraction. In contrast to the vascular smooth muscle, the skeletal muscle cells have abundant stores of calcium which is the reason why the skeletal muscle contraction is not dependent on calcium influx into the cells.

The vascular smooth muscle tone is under the influence of extra and intracellular calcium - enhancement of the calcium influx causes vasoconstriction and of the calcium efflux causes vascular relaxation. Any number of vasoactive substances can trigger vascular contraction and local factors/hormones modulate receptor-dependent processes (Figure 4). A common pathway for these responses is the transport of calcium across the cell membrane. A rise in the intracellular calcium sets the stage for vasoconstriction - when the cytosolic Ca++ rises to 10^{-6}M calcium binds to calmodulin and this interaction activates the enzyme myosin kinase which phosphorylates the light chain of myosin allowing its interaction with actin, thereby leading to arteriolar contraction (Adelstein and Hathway 1979)(Figure 5).

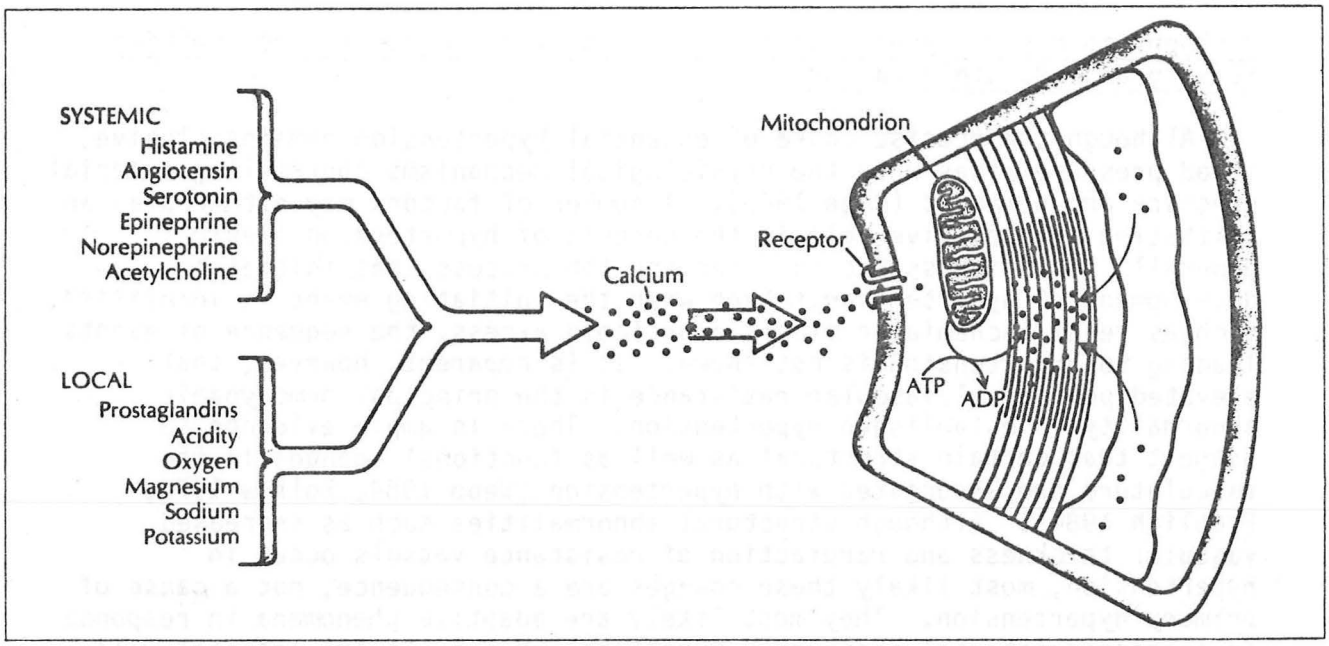


Figure 4: According to current theories, any of a number of vasoactive hormones may stimulate vascular smooth muscle contraction, and local factors may influence such receptor-dependent responses. But common to all postulated pathways is heightened transport of extracellular calcium across the cell membrane; the rise in intracellular calcium sets the stage for vasoconstriction.

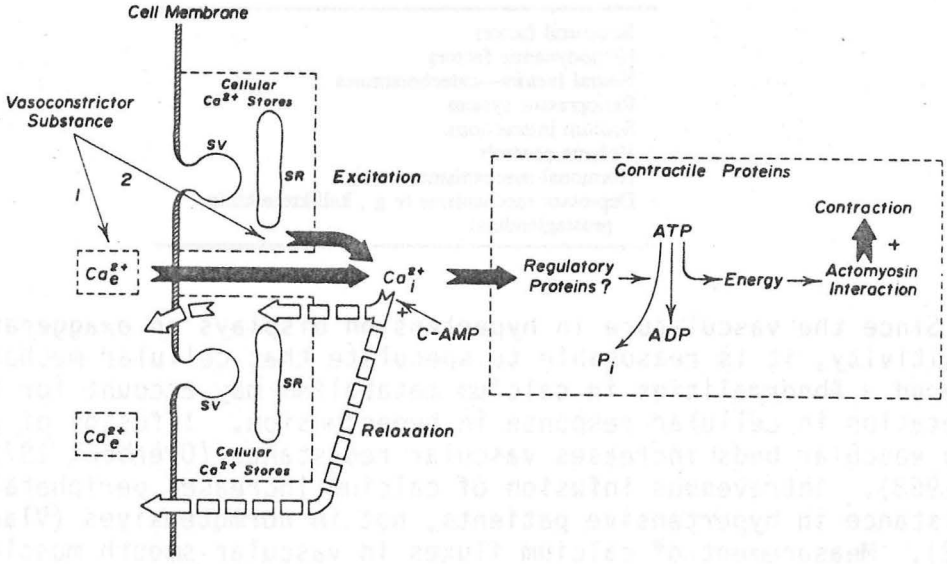


Figure 5: Major steps in excitation and contraction processes in vascular smooth muscle cells. ADP, adenosine diphosphate; ATP, adenosine triphosphate; C-AMP, adenosine 3',5'-monophosphate; e, extracellular; i, free intracellular; P_i, inorganic phosphate; SR, sarcoplasmic reticulum; SV, surface vesicles.[1] From Shepherd and Vanhoutte 1979.

Pathophysiology of Hypertension - Emerging Evidence for Altered Calcium Handing as a Possible Factor

Although the precise cause of essential hypertension remains elusive, blood pressure rises when the physiological mechanisms controlling arterial pressure are deranged (Page 1949). A number of factors may either play an initiating or a passive role in the genesis of hypertension (Table 1). Generally it is impossible to determine the process that initiates development of hypertension. Even when the initiating event is identified, such as renal ischemia or mineralocorticoid excess, the sequence of events leading to hypertension is not known. It is apparent, however, that elevated peripheral vascular resistance is the principal hemodynamic abnormality in established hypertension. There is ample evidence to suggest that certain structural as well as functional changes in the vasculature are associated with hypertension (Webb 1984, Folkow 1978, Frohlich 1984). Although structural abnormalities such as increased vascular thickness and rarefaction of resistance vessels occur in hypertension, most likely these changes are a consequence, not a cause of primary hypertension. They most likely are adaptive phenomena in response to increased arterial pressure. Functional changes in the arterial wall therefore may predispose to the development of fixed structural abnormalities. Increased or altered sensitivity to vasoconstrictor stimuli observed in clinical and experimental hypertension is perhaps the most valid explanation for possible functional vascular changes in hypertension.

TABLE 1. ***Physiological factors participating in the pathogenesis of hypertension***

Structural factors
Hemodynamic factors
Neural factors—catecholamines
Renopressor system
Sodium interactions
Volume controls
Hormonal mechanisms
Depressor mechanisms (e.g., kallikrein-kinin, prostaglandins)

Since the vasculature in hypertension displays an exaggerated sensitivity, it is reasonable to speculate that cellular mechanisms may be altered. Abnormalities in calcium metabolism may account for the alteration in cellular response in hypertension. Infusion of calcium ions into vascular beds increases vascular resistance (Overbeck 1972, Haddy et al 1963). Intravenous infusion of calcium increases peripheral vascular resistance in hypertensive patients, not in normotensives (Vlachakis et al 1982). Measurement of calcium fluxes in vascular smooth muscle suggest that there may be a leak of calcium ions through the cell membrane. The efflux of radiolabeled calcium from aortic strips of the spontaneously hypertensive rats is faster than that from the aortic strips of the normal animals (Zoster et al 1977, Bhalla et al 1978). Similar conclusions were reached based on the experimental observations that the aortic strips from SHR relax sooner than the normotensive rats when treated with a calcium antagonist, nifedipine (Pedersen 1979).

Deranged calcium binding to the cell membrane in vascular smooth muscle may account for decreased membrane stability which in turn exaggerates vascular reactivity (Table 2). It has been shown that vascular smooth muscle from hypertensive animals requires a higher calcium concentration to depress the contractile response than the normotensive controls (Hansen and Bohr 1975, Holloway and Bohr 1973). Presumably, the binding of calcium to specific loci in the membrane reduces permeability to monovalent ions and thus by affecting the membrane potential, calcium influences its own ability to permeate the membrane. So, a feature of vascular smooth muscle from hypertensive animals may be increased membrane permeability and or decreased membrane stability.

Table 2: DERANGEMENTS OF CALCIUM METABOLISM IN HYPERTENSION

1. Infusion of calcium raises the blood pressure
2. Abnormalities in calcium flux mechanisms
3. Efflux of rabiolabeled calcium from aortic strips is enhanced in SHR
4. Deranged calcium binding to the cell membrane - increased permeability/decreased stability
5. Sodium-calcium relationship Blaustein's hypothesis
6. Enhanced calcium excretion in hypertension - Strazzulo
7. ↑ Intracellular calcium in hypertensive patients

Evidence has been presented that sodium-calcium exchange mechanism may be deranged in hypertension (Blaustein 1977, Blaustein 1981). The electromechanical gradient for sodium across the cell membrane plays an important role in the modulation of intracellular calcium concentration. An increase in intracellular sodium would increase the intracellular calcium concentration. Since an increased permeability to sodium may exist in hypertension, calcium may accumulate within the cell. The increase in intracellular calcium induces or predisposes to enhanced vasoconstriction with resultant elevation of peripheral vascular resistance.

Additional evidence for an abnormality in calcium metabolism in essential hypertension was obtained by the finding of enhanced calcium excretion in hypertensive patients (Strazzulo et al 1983). These authors also noted that after intravenous calcium infusion, hypertensive patients excreted more calcium at all serum concentrations than normotensives lending support to the primary calcium leak hypothesis in hypertension. A number of probes have been used in the investigation of calcium handling abnormalities in hypertension and interpretation of the results is not simple.

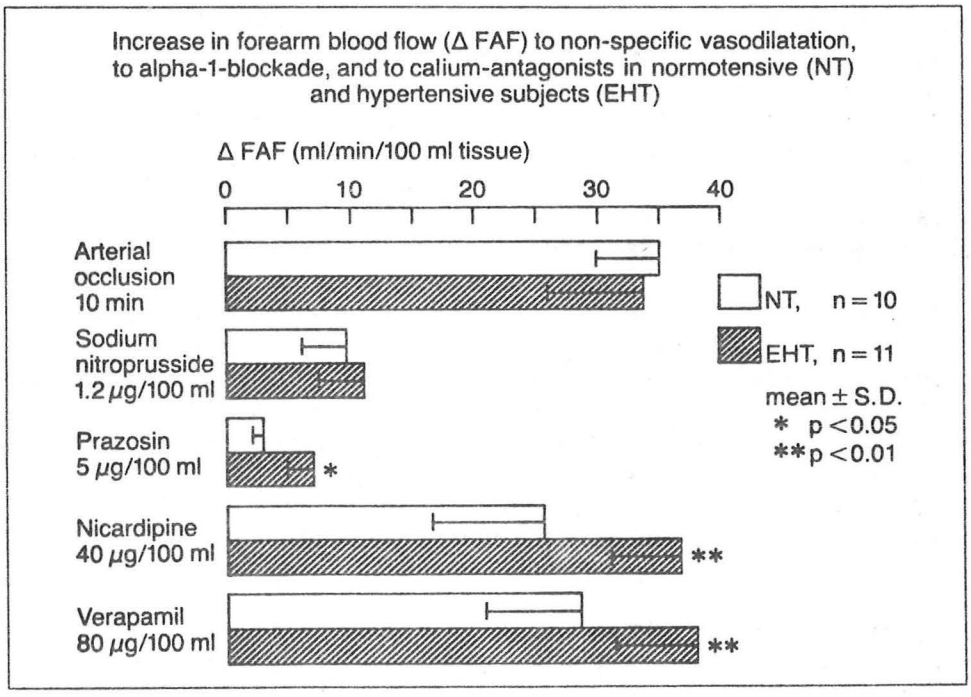
Total calcium content is increased in the arterial wall of hypertensive rats but it is not clear where the excess calcium is located (Fleckenstein 1983, Jones and Hart 1975). Ca^{45} efflux from fat cells obtained from patients with primary hypertension is considerably increased (Postonov et al 1980, Postonov and Orlov, 1984). An increase in free calcium in cells

from patients with primary hypertension as well as a remarkably close correlation between platelet calcium and arterial pressure has been reported (Zidek et al 1982, Erne et al 1984, Bruschi et al 1985)(Table 3). These studies do not reveal the cause of increased intracellular calcium but they suggest a possible relationship between raised intracellular calcium and hypertension.

INTRACELLULAR FREE CALCIUM IN PATIENTS TREATED WITH CALCIUM ANTAGONISTS
(Erne et al, 1984)

	Normotensives	Hypertensive Patients Baseline	Hypertensive Patients After Therapy
Intracellular Calcium, nM	105±16	169±36	121±32
Blood Pressure, mm Hg	-	174/109	141/87

Whatever the mechanisms of altered calcium handling may be in hypertension, they lead to certain functional consequences. For example, as alluded to already, increased intracellular calcium accumulation sensitizes to vasoactive stimuli and defective calcium binding would favor depolarization with resultant activation of the potential operated channels (Robinson, 1984). Recent studies have shed indirect light on the possible calcium handling abnormalities in essential hypertension (Robinson et al 1982, Hulthen et al 1982). The forearm resistance vessels showed an increase in dilator response to calcium channel antagonists. This can be interpreted as reflecting increased activity of the calcium channels. It may also reflect a reduced calcium efflux from the cells (Figure 6).



From Buhler et al, 1984.

It is possible but by no means proven that altered calcium handling by cell membranes may prove to be a common denominator through which peripheral vascular resistance is raised. If such a derangement in the cellular calcium metabolism is present not only in the vascular smooth muscle but also in other regulatory systems such as sympathetic nervous system and juxtaglomerular apparatus , it could account for the array of functional disturbances associated with hypertension. So far we have restricted the discussion to vasoconstrictive function of calcium. Some recent studies, however, have provided provocative data implying a vasodilatory function of calcium (McCarron et al 1981, 1982, Belizan et al 1983). The results although conflicting suggest that ionized calcium may be reduced in some patients with hypertension and that blood pressure can be lowered with calcium supplementation. These studies concerned populations with normal and/or nearly normal blood pressure levels and short-term changes in plasma calcium levels were negatively correlated with blood pressure changes. Contradictory as they are to established physiological effects and regulation of calcium, these studies in no way exclude a direct correlation between blood pressure and calcium in patients with sustained pathological elevation of arterial pressure.

Pharmacological Basis for the Use of Calcium Antagonists in Hypertension

Majority of patients with hypertension require indefinite drug therapy. Drugs which interfere with one or more of the pressor mechanisms are used with the goal of lowering the peripheral vascular resistance and restoring the physiological balance between vascular resistance and cardiac output. This is partially or completely achieved by the rational use of one or more of the antihypertensive drugs. If the blood pressure can not be reduced to a satisfactory level with optimum use of a single agent, other drugs are added as necessary. Despite the considerable therapeutic advances of the last two decades, antihypertensive drugs in use today are not always effective or free of adverse effects. Therefore, search continues to find drugs that lower the blood pressure with minimum or no adverse effects. Calcium antagonists by the nature of their mechanism(s) of action may prove to be quite useful in the treatment of hypertension and are a welcome addition to the antihypertensive drug armamentarium.

Before discussing these drugs in detail, it may be useful to review the history of calcium antagonists. In 1964 observations with two compounds - verapamil and prenylamine - revealed that their actions on isolated mammalian myocardium mimicked the effects of simple calcium withdrawal (Fleckenstein 1964). Subsequent investigations led to the belief that the negative inotropic effects of these drugs might be due to interference with calcium mediated excitation-contraction coupling of heart muscle. Similar phenomenon can be ascribed to vascular smooth muscle. A few years later it was proven that at a low extracellular calcium concentration, the effects of these drugs were increased whereas they disappeared when calcium was added to the interstial fluid leading to the designation of term calcium antagonists (Fleckenstein et al 1969).

Calcium dependent contractility is inhibited by incremental doses of nifedipine (Fleckenstein 1983) and this effect is reversible upon restoring calcium. In the lower panel of Figure 7, it is evident that nifedipine at high doses virtually abolished the contractility. The upper panel shows

Na+ dependent upstroke of the action potential which is unaffected by nifedipine. These findings emphasized and established the existence of a distinct group of drugs that inhibited the excitation - contraction coupling - the calcium antagonists. They have a greater effect on the resistance vessels than on capacitance vessels. Furthermore, their effects on different vascular beds not only depend on the sensitivity of the vessel bed but also on the contribution of the autonomic innervation to the regulation of arteriolar tone. It has been generally believed that Ca++ antagonists act by physiochemical interaction with the cell membrane; there is growing evidence to suggest their pharmacological binding to "receptors" (Towar and Schramm 1984).

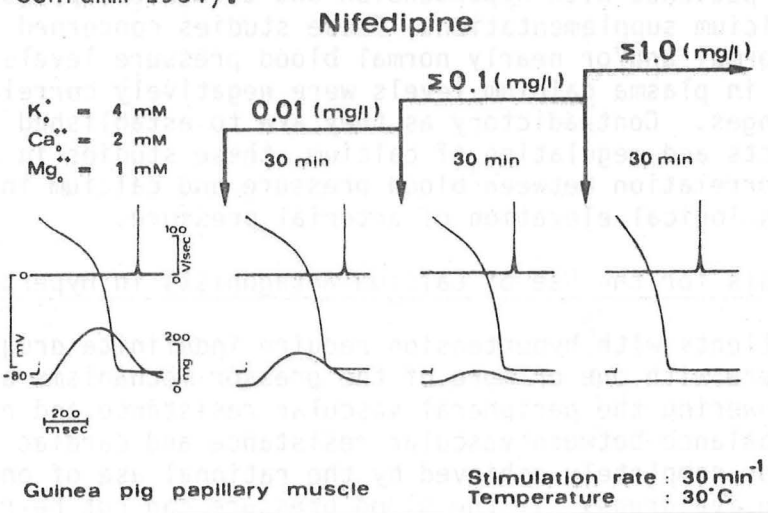


Figure 7: Complete excitation-contraction uncoupling of a guinea pig papillary muscle by a stepwise increase of the nifedipine concentration in normal Tyrode's solution from 0.01 to 0.1 and, finally, 1 mg/liter: Whereas isometric tension development was totally suppressed, the upstroke velocity of the action potentials (dV/dt_{max} = 175 V/sec) indicating the fast Na+ influx, did not change. The same was true of the height of the Na+-dependent overshoot. Potentials were measured with an intracellular microelectrode of conventional type. Isometric tensions were recorded with a mechanoelectric transducer valve.

Classification of Calcium Antagonists

To fit the original description of Fleckenstein, a drug to be classified as a calcium antagonist should inhibit voltage-activated inward displacement of Ca++ and this effect should be reversed by calcium (Figure 8). The compounds that inhibit the slow channel transport fall into 3 major categories:

I. Inorganic Blockers - eg. Ni^+, Mg++

II. Organic Blockers - eg. nifedipine, verapamil, diltazem

III. Energy Dependant Blockers - eg. cyanide, dinitrophenol

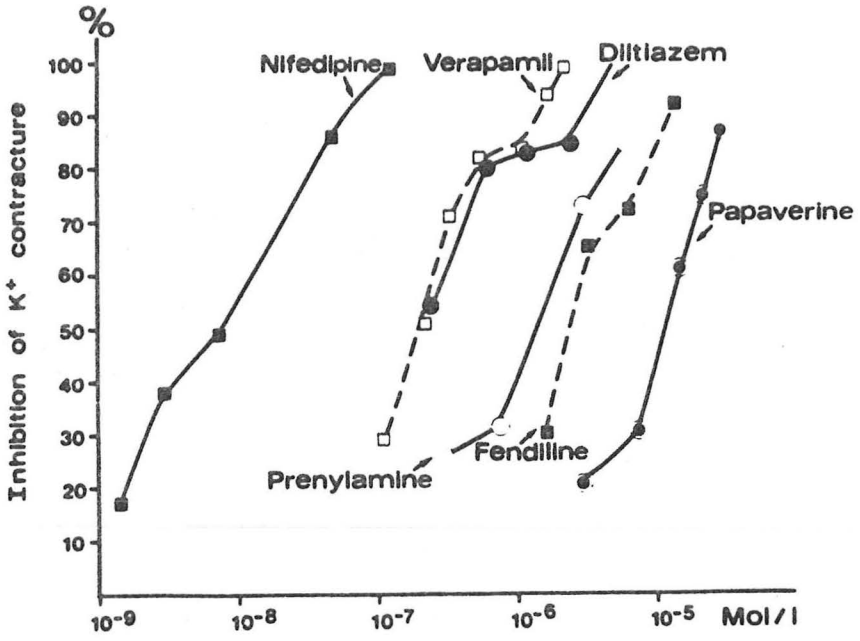


Figure 8: Suppression of K-induced coronary artery contractures by calcium antagonists. Note the potency of different calcium antagonists (From Fleckenstein 1983B)

The inorganic and energy dependent calcium blockers exhibit a host of accessory toxic effects precluding any therapeutic use.

The organic blockers are further classified on the basis of their chemical structure:

(1) Papaverine derivatives - eg. verapmail, D600 (Gallopamil)
(2) Dihydropyridines - eg. Nifedipine, nitrendipine
(3) Benzothiazepines - eg. Diltiazem
(4) Piperavine derivatives - eg. Cinnarizine

Fleckenstein prefers a more simple A and B classification based on the potency and specificity of the agent:

Group A: Substances of outstanding calcium antagonistic potency - eg. nifedipine, verapamil, gallopamil, or diltiazem

Group B: Substances of calcium antagonistic properties that are less potent and less specific than those of group A. eg. prenylamine, fendiline, perhexeline

Although they share the common property of inhibiting the slow calcium current, calcium antagonists have disparate effects on the vascular smooth muscle, cardiac conduction, and myocardium. It appears that the effects may also vary from one vascular bed to the other. The consequences of slow channel inhibition are shown in Figure 9.

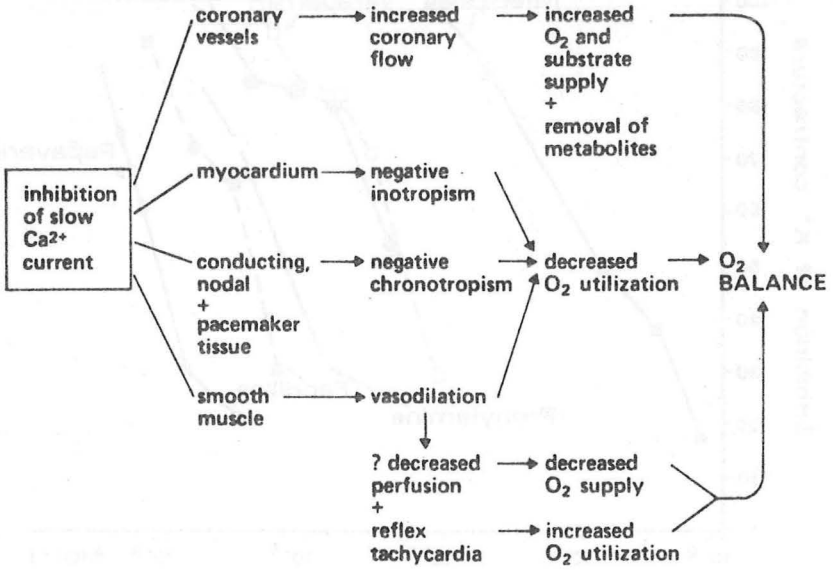


Figure 9: Consequences of slow-channel inhibition in the circulation.

Mechanism(s) of Action of Calcium Antagonists in Hypertension

The mechanisms whereby calcium antagonists are effective in the treatment of hypertension are complex. Since the chemical structure of these compounds is heterogenous, it is unlikely that all the calcium antagonists act in the same fashion at the molecular level although the net effect may be common, i.e. inhibition of calcium action. The basic contraction-relaxation phase in vascular smooth muscle is dependent on a rise and fall of internal calcium concentration and inhibition can take place at various steps in this pathway. The precise mechanism whereby calcium antagonists mediate vascular relaxation is unclear, but the possibilities are shown in Table 4:

Table 4: MECHANISM OF ACTION OF CALCIUM ANTAGONISTS

- Inhibition of calcium influx
- Inhibition of intracellular calcium release
- Stimulation of calcium efflux
- Effects on Calmodulin
- ? Binding to receptors
- Inhibition of α_2-adrenoreceptor mediated vasoconstriction

There is growing evidence to suggest that the action of calcium antagonists involves interaction of these drugs with specific binding sites which are probably calcium channels themselves or proteins associated with

calcium channels (Cohen et al 1984). Other sites of action are possible (Zoster and Church 1983, Cauvin et al 1983, Nayler and Phoole-Wilson 1981) and it appears that the mode of action of these agents at the cellular level is more complex than that of "simple plugging of the channel" (Figure 10). For example, verapamil preferentially blocks the channel in the open (activated) state where as dihydropyridines like nifedipine show little or no selectivity among the several states of the calcium channel (Schwartz 1984). Similarly diltiazem binds preferentially in the open (and inactivated) state (Van Breemen et al 1984).

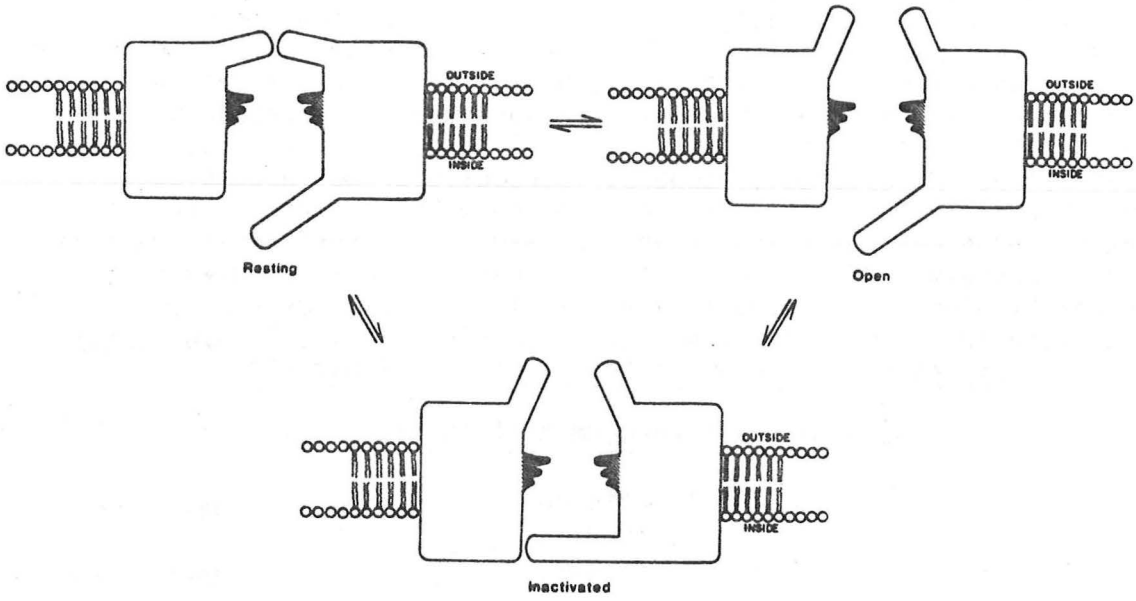


Figure 10: In the resting channel, the activation gate is closed while the inactivation gate is open. A change in transmembrane potential initially opens the activation gate, thereby allowing ions to pass through the open channel. Subsequent closure of the inactivation gate causes the channel to become inactivated. Termination of the refractory state of the inactivated channel occurs when return to resting potential causes the inactivation gate to reopen and the activation gate to close. From Katz 1985.

Measurements of free calcium suggest that nifedipine lowers intracellular calcium activity in patients with hypertension (Zidek et al 1982, Erne et al 1984). Treatment with verapamil has been shown both in vivo and in vitro to reverse the leucocyte transport defect in hypertension (Gray et al 1985, Gray et al 1984). This further supports the hypothesis that sodium and calcium may be closely linked in the pathophysiology of hypertension. There is some information that the antihypertensive action of verapamil is modulated by the prostaglandin system (Das, 1982). It has been shown that calcium antagonists interfere with the function of post-synaptic alpha$_2$-adrenoceptors (Van Zweiten et al 1983, Pedrinelli and Tarazi 1984). However, a direct interaction between calcium antagonists and adrenergic receptors has not been documented due to limited affinity of these drugs for alpha$_2$-adrenoreceptor.

While the mechanism of action of calcium antagonists in hypertension appears to be clearly related to their ability to inhibit the intracellular actions of calcium on vascular smooth muscle, the precise location of the site in uncertain and perhaps is different for each class of calcium channel antagonists. Ongoing studies utilizing sophisticated radiological binding techniques may clarify or even sub-classify the sites of the action of these drugs.

Clinical Use of Calcium Antagonists in the Treatment of Hypertension

Elevated peripheral vascular resistance is the dominant hemodynamic abnormality in chronic hypertension. The ability of calcium antagonists to relax the vascular smooth muscle and therefore to decrease the peripheral vascular resistance makes them potentially useful as antihypertensive drugs. Evidence that calcium ion fluxes are abnormally regulated in hypertension lends further credence to the utility of calcium antagonists in this condition. As covered elsewhere, intracellular Na^+ accumulation causes an increase in the cyctosolic calcium concentration which leads to functional disturbances resulting in an increase in the peripheral vascular resistance (Blaustein, 1977). The focus of today's discussion will be mainly on the hypotensive actions of three well known calcium antagonists - nifedipine, verapamil, and diltiazem (Table 5) (Figure 11). None of these drugs is currently approved by FDA for the treatment of hypertension.

Table 5: MAIN CALCIUM ANTAGONISTS

1. Nifedipine
2. Verapamil
3. Diltiazem

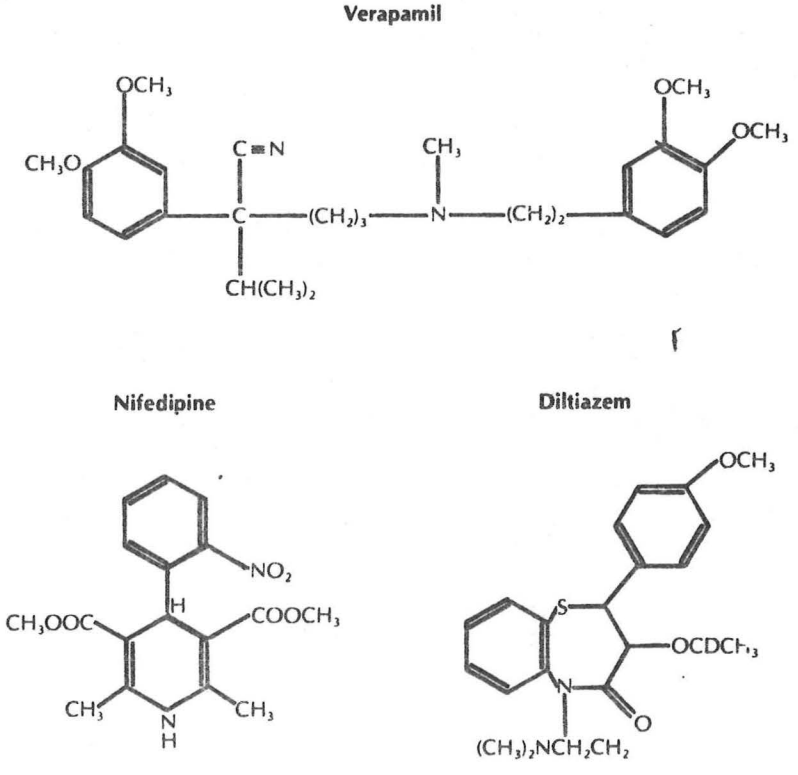


Figure 11: Structural formulas of verapamil, nifedipine and diltiazem

Nifedipine

Nifedipine is a dihydropyridine derivative and is a potent relaxant of vascular smooth muscle. Its dominant effects are discernible in the peripheral vasculature. The fall in vascular resistance induced by nifedipine is accompanied by reflex activation of sympathetic tone.

Table 6: EFFICACY OF NIFEDIPINE IN HYPERTENSION

- Acute effects
- Chronic effects
- Monotherapy
- In combination with other antihypertensive drugs
- In comparison to other antihypertensive drugs

Acute Therapy: The rapid onset of action of nifedipine given orally or sublingually makes it eminently suitable for the emergency treatment of hypertension. At the present time, acute management of hypertension usually, but not invariably requires parenteral therapy. Although orally active agents like clonidine, captopril, and minoxidil are sometimes used for acute blood pressure reduction, their effects are not consistent. Administration of nifedipine orally or sublingually to hypertensive patients causes a significant reduction of both the systolic and diastolic blood pressure in the supine and upright positions. Hypotensive effects are seen within 1-5 minutes after sublingual and 10-20 minutes after oral administration (Guazzi et al 1977). Depending on the dose, the maximum response is seen 20-40 minutes and the blood pressure gradually returns to original levels in 3-8 hours. Most studies have used nifedipine in doses between 10-30 mg. Even a 5 mg dose has been shown to produce significant reduction in the blood pressure acutely (MacGregor et al 1983).

The magnitude of blood pressure response in relation to pretreatment level is shown in Figure 12 which is a compilation of data from several publications (Beer et al 1981, Corea et al 1979, Guazzi et al 1977, Kuwajima et al 1977, Pedersen and Mikkelsen 1978, Olivari et al 1979). There is a close correlation between the reduction in blood pressure and the values before treatment. While nifedipine does not ordinarily lower the blood pressure in normotensive individuals, even a very low dose reduces elevated blood pressure promptly.

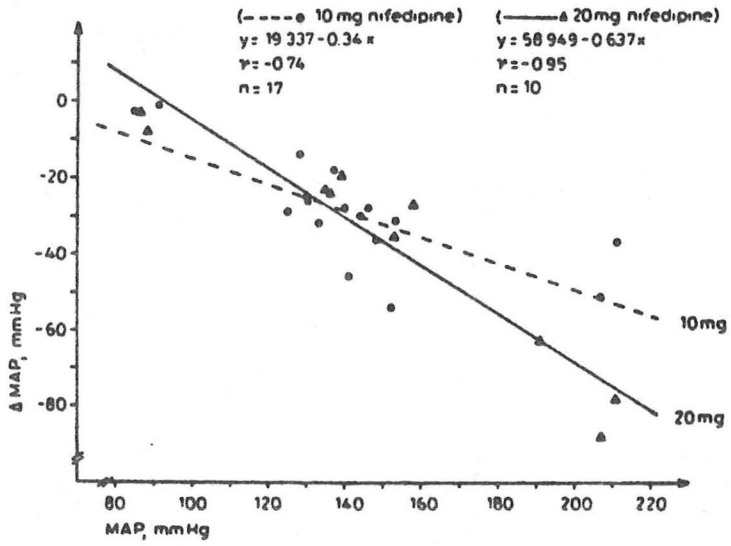


Figure 12: The magnitude of fall in blood pressure from nifedipine is clearly dependent on the baseline blood pressure. The regression line was drawn from 14 publications. From Heidland et al 1982.

In one recent study (Erbel et al 1983) administration of a single 20 mg nifedipine to 30 patients with severe hypertension reduced the blood pressure from 235±16/123±16 to 210±23/110±17 in 10 minutes. Only 4 patients failed to show any response. Surprisingly, the heart rate did not change much, a finding that is not uniform. Similarily, oral administration of 10-20 mg nifedipine in 25 patients with hypertensive crisis lowered the average blood pressure by 70/36 mm Hg (Bertel et al 1983) (Figure 13). In this study, the cerebral blood flow increased in a small number of patients whereas in comparison, clonidine reduced the cerebral blood flow. Acute nifedipine administration has also been reported to ameliorate severe hypertension in children (Dilmen et al 1983) and in pregnancy (Walters and Redman 1984).

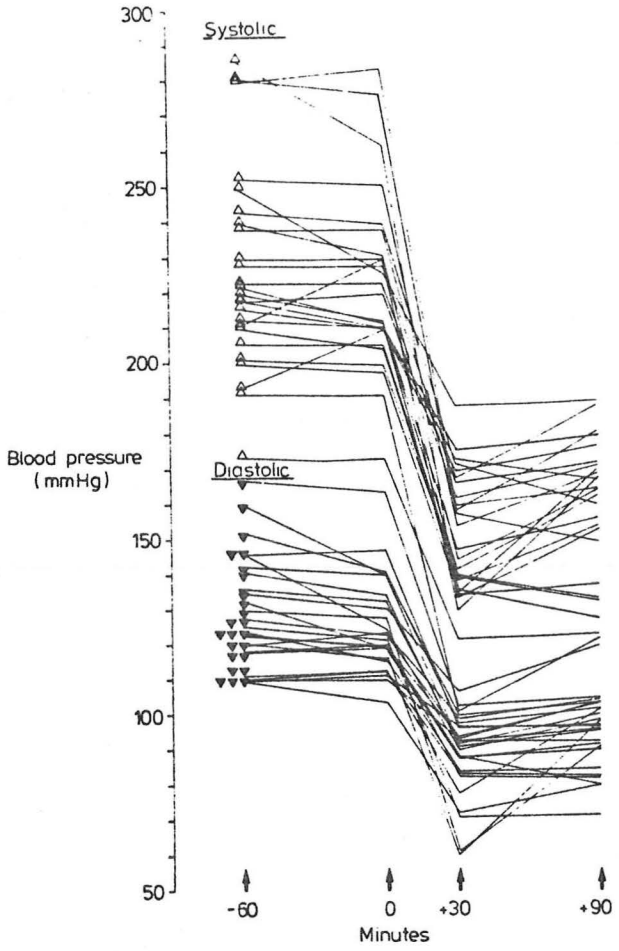


Figure 13: Effect of 10-20 mg nifedipine by mouth in hypertensive emergencies (n=25). From Bertel et al 1983.

The immediate hypotensive effect of nifedipine is not related to the etiology of hypertension; the blood pressure reduction is seen in hypertension of various causes (Aoki et al 1976). The heart rate response to acute treatment with nifedipine is variable and is probably dependent on the dose and magnitude of blood pressure reduction. When tachycardia does develop, its duration is less than that of the blood pressure reduction (Heidland et al 1982). Since the heart rate response is not as predictable as that seen with other direct vasodilators, one can not prejudge the need for concomitant beta-blockade. Moreover, the safety of combined treatment in acute clinical situations where the patients' hemodynamic and reflexive mechanisms may already be compromised can not be determined. Younger patients may show a greater increase in the heart rate suggesting age-dependent beta-adrenergic responsiveness to reflex sympathetic stimulation (Bertel 1983). Unlike other potent direct vasodilators, nifedipine may actually promote sodium excretion and diuresis (Klutsch et al 1972). Table 7 is a compilation of some clinical studies which showed the effectiveness of nifedipine in lowering the blood pressure acutely.

Table 7: Nifedipine Single Dose Studies in Hypertensive Emergencies and Severe Hypertension

Study (Ref)	No. Patients	Single Oral Dose (mg); Route of Administration	Mean Blood Pressure Pre-treatment		Mean Blood Pressure Post-treatment (30 minutes)			
			Supine (mm Hg)	Pulse Rate (beats/min)	Supine (mm Hg)	Pulse Rate (beats/min)	Pulse Rate (beats/min)	Decline in Blood Pressure (mm Hg)
Aoki et al 1978	9	30;--	167/113	70	122/81	82	+12	45/32
Beer et al 1981	17	10;SL	172/109	--	140/88	--	--	32/21
Beer et al 1981	26	20;SL	204/128	76	160/97	89	+13	44/31
Bertel et al 1983	25	20;PO	221/126	74	152/89	84	+10	69/37
Guazzi et al 1977	3	60;SL	307/164	--	248/112	--	--	59/52
Kuwajima et al 1982	6	10;PO	237/110	89	150/73	87	-2	87/34
Kuwajima et al 1982	12	10;PO	205/113	72	162/92	80	+8	43/21
Polese et al 1979	7	10;PO	221/120	88	177/94	96	+8	44/26
Haft et al 1984	43	10;SL	205/122	--	158/88	--	--	47/34

In the treatment of hypertensive emergencies, the blood pressure level alone should not be the criterion for acute lowering of the blood pressure (Ram 1984). Severe uncontrolled hypertension in a relatively asymptomatic patient with no evidence of ongoing target organ dysfunction does not constitute an indication for acute treatment. One must make the distinction between critical and non-critical elevation in blood pressure based upon clinical evaluation of the patients. This point must be borne when analyzing the publications reporting treatment of hypertensive "emergencies" with nifedipine or other agents.

In the treatment of hypertensive encephalopathy which is a distinct clinico-pathalogical entity, administration of nifedipine resulted in improvement of the presenting CNS manifestations (Kuwajima et al 1977, Guazzi et al 1977). Sometimes progression of the underlying process has been noted (Nobile-Orazio and Sterzi 1981). Nifedipine appears to be quite effective in treating pulmonary edema associated with severe hypertension (Polese et al 1979).

The advantages of nifedpine in the acute treatment of hypertension are avoidance of parenteral therapy (and the attendant need for constant monitoring), rapid onset of action, favorable (stable) hemodynamic response, and absence of CNS effects provided that the drop in blood pressure is not too pronounced. Although immediate therapy with nifedipine in patients receiving other anti-hypertensive drugs may be risky, in a recent study no untoward responses occured in this setting (Haft and Litterer 1984). Nevertheless, proper precautions must be undertaken in such circumstances. While using nifedipine for rapid blood pressure control, usual precautions practiced for the care of patients with severe,

complicated hypertension must be adhered. Rarely, unwanted degree of hypotension may occur; in a patient with malignant hypertension the blood pressure dropped to 80/60 from 250/150 mm Hg after a single 10 mg oral dose of nifedipine (Heidland et al 1982). Asking the patient to chew or to crush the capsule leaves an unpleasnt aftertaste. So it is advisable to puncture the capusle, the contents of which can be absorbed sublingually. Although nifedipine therapy for acute management of hypertension provides a potentially beneficial and convenient alternative to the currently practiced modalities, it does not absolve the physicians from observing the patient closely at least for the first few hours.

Long-term Therapy With Nifedipine

Effectiveness of nifedipine in the chronic treatment of hypertension has been documented in several studies (Corea et al 1979, Pedersen and Mikkelson 1978, Murphy et al 1983, Masotti et al 1984, Olivari et al 1979, Yoshimura et al 1983, Hornung et al 1983, Brennan et al 1983) (Table 8) (Figure 14). Most of these studies were conducted for 3-12 week periods and the doses ranged from 20-80 mg/day. In contrast to the acute studies, there was no clear-cut dose response relationship. The maximum anti-hypertensive effect was seen only after several days of treatment and the blood pressure tended to return to baseline within 1-2 days of discontinuation of the drug (Guazzi et al 1980, Olivari et al 1979). In most long term studies, heart rate was either unchanged or decreased (Ekelund and Oro 1979, Murakami et al 1972, Corea et al 1979). Cardiac output is increased either due to a reduction in the afterload and/or due to activation of sympathetic tone. Unlike other direct vasodilators, nifedipine does not cause generalized fluid retention (Pedersen and Mikkelsen 1978, Olivari et al 1979, Guazzi et al 1980). Plasma volume expansion has not been reported with chronic nifedipine therapy. This may be due to the fact that nifedipine may exert a slight natriuretic effect either directly or via inhibition of aldosterone secretion. Chronic nifedipine administration does not cause postural hypotension (Corea et al 1980, Olivari et al 1979).

Table 8

SHORT-TERM NIFEDIPINE MONOTHERAPY

Study (Ref)	No. Patients	Maximal Oral Dose (mg/day)	Duration of Therapy (wks)	Average Supine Blood Pressure (mm Hg) Pretreatment	Post treatment	Decline in Blood Pressure (mm Hg)
Ekelund et al 1982	14	30	4	178/99	158/88	20/11
Eggertsen et al 1982	13	30	12	157/106	148/96	9/10
Hornung et al 1983	15	120	8	175/98	141/80	34/18
Gould et al 1982	9	120	6	182/106	148/86	34/20
Midtbo et al 1982	28	40	6	149/107	133/93	16/14
Murakami et al 1972	7	30	1	164/98	138/84	26/14
Olivari et al 1979	14	20	3	190/117	158/97	32/20
Olivari et al 1979	13	40	3	205/118	165/97	40/21
Klein et al 1983	20	60	8	152/106	140/91	12/15

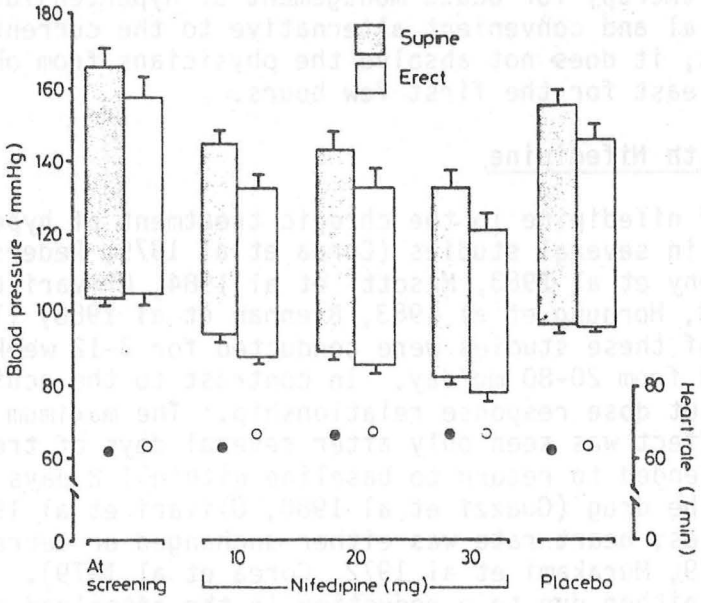


Figure 14: Mean (SEM) supine and erect blood pressure and heart rate in 14 patients before and after treatment with nifedipine 10,20, and 30 mg three times daily. From Murphy et al 1983.

Although total experience is limited, nifedipine monotherapy is effective in the treatment of hypertension. This is not associated with unfavorable effects that are known to occur with conventional direct arteriolar dilators.

Nifedipine in Combination With Other Antihypertensive Drugs

i) Nifedipine plus propranolol:

The effects of nifedipine in hypertensive patients can be enhanced by propranolol (Aoki et al 1978, Imai et al 1980, Yagil et al 1983) (Figures 15 and 16). Combined treatment reduced the unwanted consequence of sympathetic activation - palpitations, flushing, headache. Long term safety of combining nifedipine with beta-blockers is not known. It is advisable to add a beta-blocker if reflex tachycardia is present. Besides propranolol, other beta-blockers such as metoprolol and pindolol have been successfully used along with nifedipine with beneficial outcome (Eggertsen and Hansson 1982, Tsukiyama et al 1984, Ekelund et al 1982).

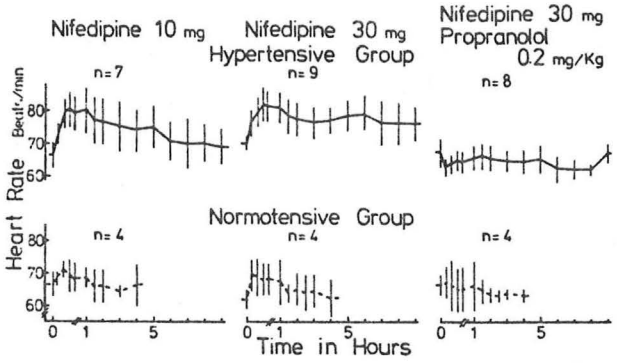


Figure 15: Heart rate increase with nifedipine in normotensive volunteers and hypertensive patients. Combined administration of nifedipine and propranolol does not result in an increase in heart rate. Propranolol may inhibit the increase of the nifedipine-induced increase in heart rate. Hypertensive patients = (——); normotensive volunteers = (----). Values are mean ± standard deviation. From Aoki et al 1978.

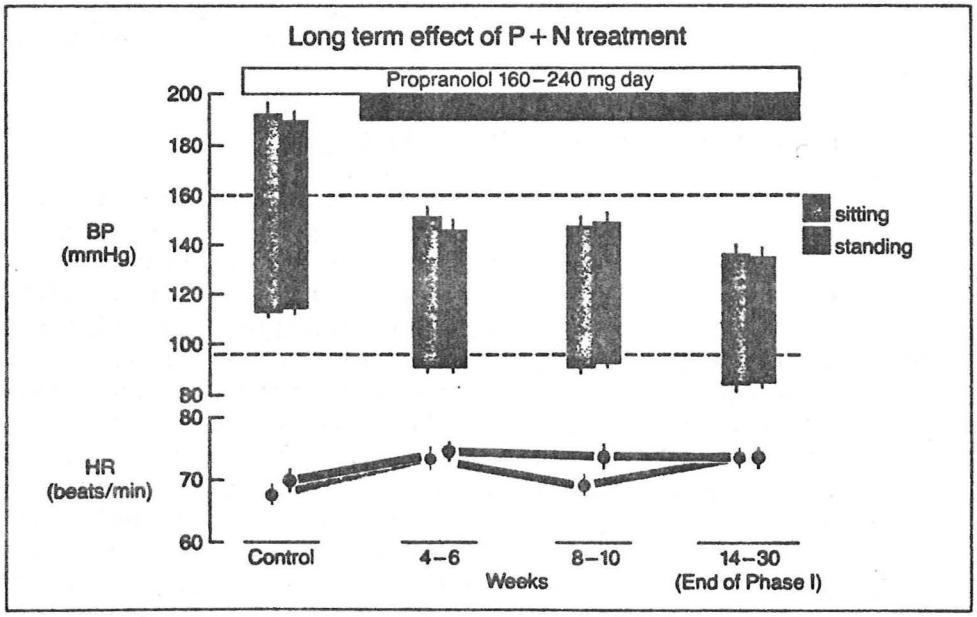


Figure 16: Adapted from Yagil et al 1983.

ii) Nifedipine with diuretics:

As is the case with other non-diuretic agents, the efficacy of nifedipine appears to be enhanced by co-administration of a diuretic (Hallin et al 1983) but experience with this combination is limited.

iii) Nifedpine with methyldopa:

In a carefully conducted study, addition of methyldopa to patients not responding to nifedipine resulted in additional blood pressure reduction (Guazzi et al 1980). Hemodynamic observations showed significant reduction in heart rate and peripheral vascular resistance. Interestingly, the combination treatment also decreased the pulmonary arterial pressures.

iv) Nifedipine and clonidine:

In a limited study with a small number of patients, hypotensive effects of nifedipine and clonidine were found to be additive (Imai et al 1980).

v) Nifedipine and captopril:

In patients with severe hypertension, nifedipine (40 mg/day) and captopril (100 mg/day) combination was shown to be effective with salutary hemodynamic effects (Guazzi et al 1984). Plasma renin activity which increased with captopril reverted to baseline after adding nifedipine, suggesting a possible effect of the latter on renin release mechanism.

vi) Nifedipine and prazosin:

Administration of nifedipine with prazosin has been reported to cause severe hypotension indicating that combined use of these two drugs may be harmful (Jee and Opie 1983).

Nifedipine in the Treatment of Refractory Hypertension

Nifedipine is a useful agent for the treatment of drug resistant hypertension. In fact, at the present time refractory hypertension constitutes the most common indication for the use of nifedipine in hypertension. Currently, patients not responding to multiple conventional drugs are considered for minoxidil or captopril therapy. In this setting, nifedipine offers an attractive treatment alternative (Table 9). Preliminary experience suggests that nifedipine is effective as a third line agent in drug resistant hypertension (Dean and Kendall 1983, Murphy et al 1983, Sloan and Beevers 1983)(Figure 17). A logical regimen for the treatment of poorly controlled hypertension would be a diuretic plus beta-blocker plus nifedipine. Beta-blockers in this setting not only complement the hypotensive action of nifedipine but they also offset the activation of sympathetic tone. The advantages of nifedipine over other drugs include a possible beneficial effect on cerebral and coronary circulations. For women, nifedipine offers a clear advantage over minoxidil because the latter causes hypertrichosis, an unacceptable cosmetic effect. Nifedipine is also a good alternative for patients who might be at a risk of developing captopril induced toxic effects. Further long term studies will be necessary to determine whether the ultimate prognosis in severe/resistant hypertension is any better if treated with nifedipine compared to other drugs.

Table 9

Comparison of drugs used in resistant hypertension

Effect	Drug		
	Minoxidil	Captopril	Nifedipine
Efficacy	+++	++	++
Simplicity of administration	No	Yes	?
Long-term effects	Good	Good	Not known
Concomitant drugs	Diuretic + beta blocker	Diuretic	Diuretic ± beta blocker
Patient acceptance	Uncertain	Good	Uncertain
Use in heart failure	No	Yes	—
Reflex tachycardia	++	—	+
Fluid retention	++	—	+
Hirsutism	Yes	No	No
Toxicity	—	Renal, hematologic	—

Source: Prepared for Modern Medicine *by C.V.S. Ram, MD*

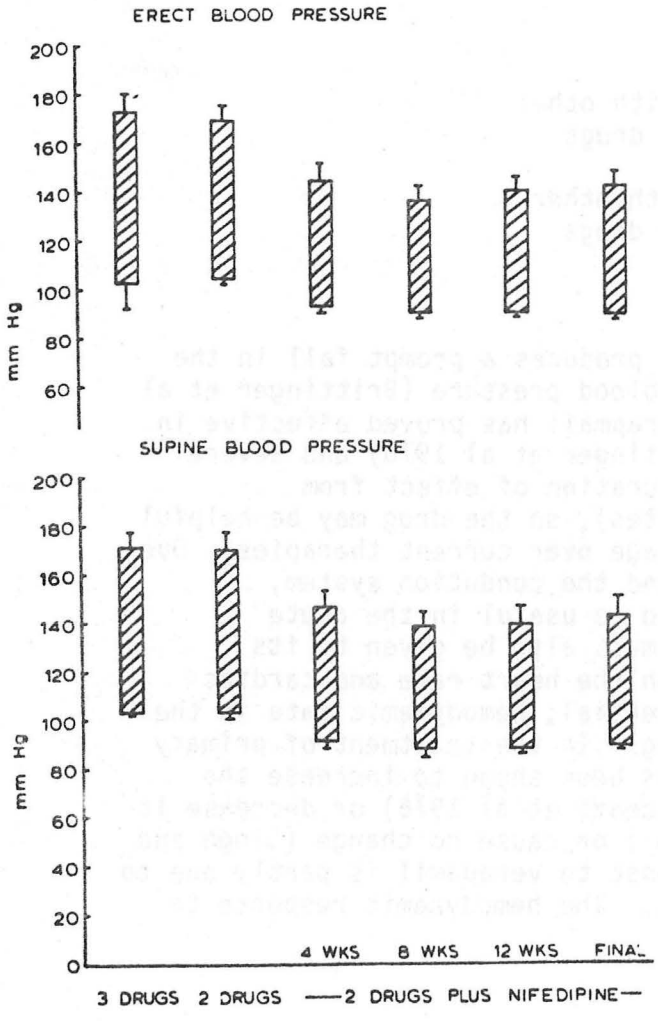


Figure 17: Erect and supine blood pressures (mean±SEM) on previous regimen, on beta-blocker and diuretic and after the addition of nifedipine. From Dean & Kendall 1983.

Nifedipine in the Treatment of Renovascular Hypertension: Treatment of renovascular hypertension with nifedipine has been shown to be effective in a small series (Rosenthal T, 1985); with nifedipine the blood pressure decreased to 137/81 from 175/109 mm Hg. The effectiveness of nifedipine in renovascular hypertension implies the role of calcium in the regulation of renin-angiotensin-system.

Nifedipine in Chronic Renal Failure: There is no systematic experience with nifedipine in patients with reduced renal function. In short term studies, nifedipine therapy resulted in improved control of hypertension without untoward renal effects (Eliahou et al 1982, Kubo et al 1983).

Verapamil

Verapamil is structurally related to papaverine. Besides direct relaxation of vascular smooth muscle, it has an effect on the A-V conduction and inotropy. Although the antihypertensive effects of verapamil were recognized more than 20 years ago, its therapeutic potential has been more thoroughly realized in the recent years.

Table 10: EFFICACY OF VERAPAMIL IN HYPERTENSION

- Acute effects
- Chronic effects
- Monotherapy
- In combination with other antihypertensive drugs
- In comparison with other antihypertensive drugs

Acute Effects of Verapamil

Parenteral administration of verapamil produces a prompt fall in the peripheral vascular resistance and in the blood pressure (Brittinger et al 1970, Heidland et al 1962). Parenteral verapmail has proved effective in the treatment of hypertensive crisis (Brittinger et al 1970) and severe hypertension (Bhat and Wasir 1982). The duration of effect from intravenous injection is short (10-20 minutes), so the drug may be helpful only as an infusion which offers no advantage over current therapies. Due to its inhibitory effect on the A-V-node and the condution system, parenteral verapamil therapy is unlikely to be useful in the acute management of hypertension; consideration must also be given to its negative inotropic effects. The effects on the heart rate and cardiac output of parenteral verapamil are controversial; hemodynamic data in the treatment of acute hypertension are lacking. In the treatment of primary cardiac disorders, parenteral verapamil has been shown to increase the heart rate (Attenhog and Ekelund 1975, Vincenzi et al 1976) or decrease it (Frishman et al 1982, Andrasean et al 1975) or cause no change (Singh and Roche 1977, Ferlinz 1981). Variable response to verapamil is partly due to different dosages in different populations. The hemodynamic response to

verapamil is dependent on the complex interation of the drug's negative and chronotropic effects, coronary, and peripheral vasodilation, and inhibitory effect on the conduction system. Nevertheless, most agree that verapamil reducs left ventricular contractility and must be used with extreme caution in patients with compromized left ventricular function. Althouth the peripheral vasodilation produced by verapamil is expected to decrease the afterload and improve the pump function, this property can not be relied upon to overcome its negative inotropic effect.

Long-term Therapy with Verapamil in Hypertension

In a number of clinical trials, chronic therapy with verapmail produced a dose dependent reduction in the blood pressure without causing tachycardia (Leonetti et al 1980, Lewis et al 1978, Midtbo et al 1980) (Table 11). In uncomplicated hypertension, nifedipine and verapamil appear to produce similar anti-hypertensive effects. Due to extensive hepatic extraction, bioavailability of verapamil is considerably less than that of nifedipine (Henry, 1980).

Table 11

SHORT-TERM VERAPAMIL MONOTHERAPY

Study (Ref)	No. Patients	Maximal Oral Dose (mg/day)	Duration of Therapy (wks)	Average Supine Blood Pressure (mm Hg) Pretreatment	Post Treatment	Decline in Blood Pressure (mm Hg)
Frishman et al 1982	12	480	3	158/98	144/88	24/10
Anavekar et al 1982	9	320	6	174/111	154/89	20/22
Lowis et al 1979	26	480	--	201/114	164/87	37/27
Gould et al 1982	16	480	6	182/105	149/82	33/23
Midtbo et al 1980	23	480	4	154/104	144/94	10/10
Leonetti et al 1980	12	480	1	177/111	150/96	27/15
de Leeuw et al 1982	15	480	1	170/100	140/81	30/19

In hypertensive patients, the blood pressure was reduced by 10% after oral administration of verapamil 80 mg t.i.d. (Leonetti et al 1980, Lewis et al 1979). Incremental doses upto 120 mg t.i.d. induced additional falls in the blood pressure (Figure 18). In one study the response to verapamil was inversely related to the renin levels and directly proportional to the age (Buhler et al 1982) (Figures 19 and 20).

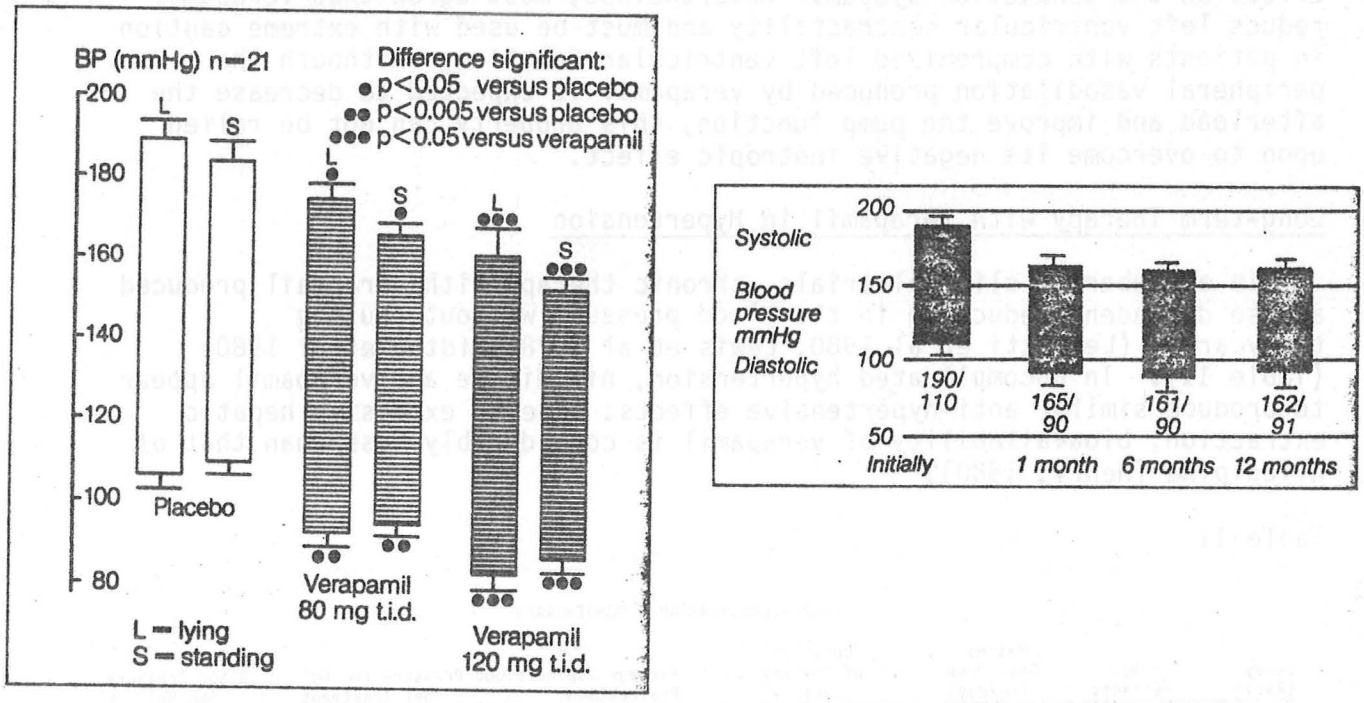


Figure 18: Short term (left panel) and prolonged treatement (right panel) with verapamil in hypertension. Adapted from Lewis et al 1978,1979.

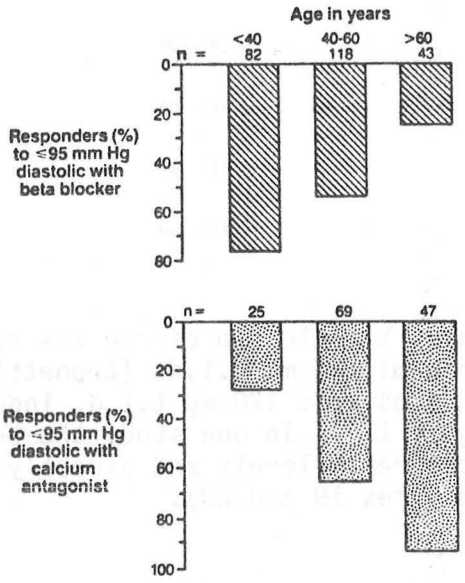


Figure 19: Fraction of patients with a diastolic blood pressure of 95 mm Hg or greater during antihypertensive therapy with beta blockers (top) or calcium entry blockers (bottom) in three age groups with essential hypertension. From Buhler et al, Am J Med, August 20, 1984:36-42.

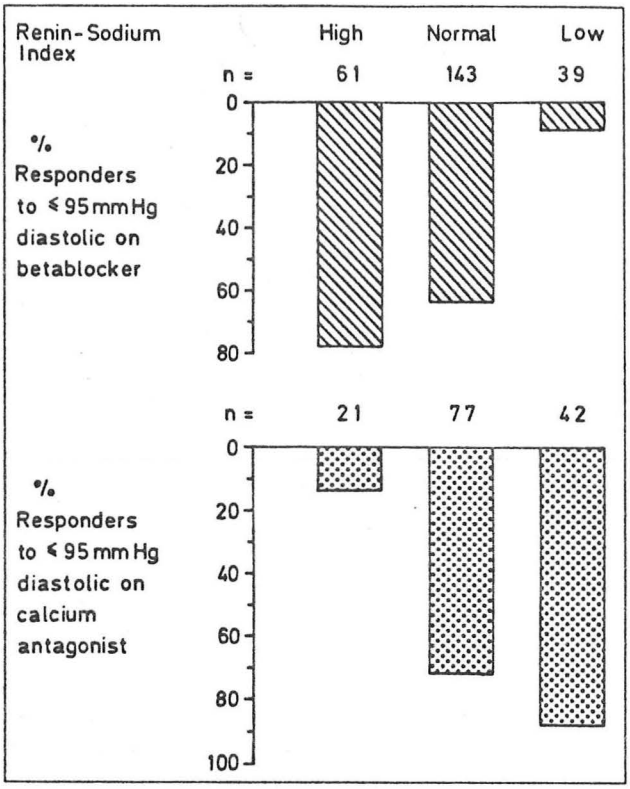


Figure 20: Fraction of patients with a diastolic blood pressure of 95 mm Hg or less during antihypertensive therapy with beta blockers (upper panel) or calcium entry blockers (lower panel) in the three renin subgroups. From Buhler et al. Am J Med, August 20, 1984: 36-42.

In moderate hypertension, verapamil 240-480 mg daily reduced the blood pressure from 177/111 to 150/96 within 10 days of treatment (Leonetti et al 1980). The immediate and long-term effects of verapamil in uncomplicated hypertension suggest that tolerance is not seen (Muiesen et al 1981). Oral verapamil reduced the blood pressure within 1 hour and the effect persisted for 4 hours, with continuous therapy for 2-3 months, the blood pressure fell from 165/100 to 136/92 on verapamil 80 mg t.i.d.. In a short term study (DeLeeuw et al 1981), verapamil (40-160 mg t.i.d.) reduced both the peripheral and renal vascualr resistance. In another study, blood pressure response was analyzed by intra-arterial mointoring after 6 weeks of therapy with verapamil 120-160 mg t.i.d. The drug produced impressive blood pressure reduction throughout the 24 hour period (Gould et al 1982) (Figure 21). Heart rate was lowered with treatment. In a small study (6 patients), verapamil failed to lower the blood pressure despite a high dose (Lederballe-Pedersen 1978).

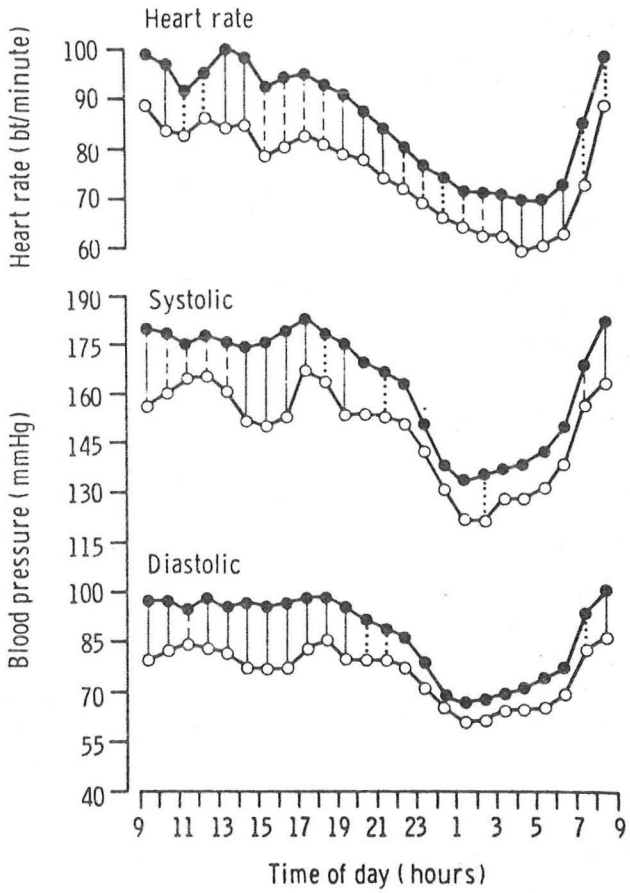


Figure 21: Circadian curves derived from hourly mean values of heart rate, and systolic and diastolic blood pressure before (•) and after (o) verapamil. Vertical lines between curves indicate $p < 0.05$ (....), $p < 0.01$ (- - -), or $p < 0.001$ (————). From Gould et al 1982.

Chronic verapamil administration is not accompanied by increased renin activity (Leonetti et al 1980). Verapamil was found to be effective in the management of renal hypertension (Wigler et al 1984). In fifteen patients with uncomplicated hypertension, verapamil therapy resulted in increased excretion of sodium and suppression of plasma aldosterone levels (deLeeuw and Birkenhager 1984). The blood pressure reduction caused by verapamil was sustained during exercise and no increase in the heart rate was noted (Lund-Johansen 1984). Substitution of verapamil for hydralazine in patients with severe hypertension resulted in effective blood pressure control (Gonzalez-Gomez 1983).

Comparison of Verapamil with Other Drugs

Several comparative studies suggest that verapamil is as effective as propranolol in the long term management of hypertension (Frishman et al 1982, Halperin et al 1984, Leonetti et al 1984) (Figure 22). Similar results were obtained when verapamil was compared to pindolol (Doyle 1983) and labetalol (Anavekar et al 1982). Therefore, verapamil may be a useful first line drug in the treatment of hypertension particularly when beta-blockers are contraindicated or not tolerated. It appears that verapamil may have an advantage over propranolol because of the absence of metabolic adverse effects seen with the latter (Leonetti et al 1984).

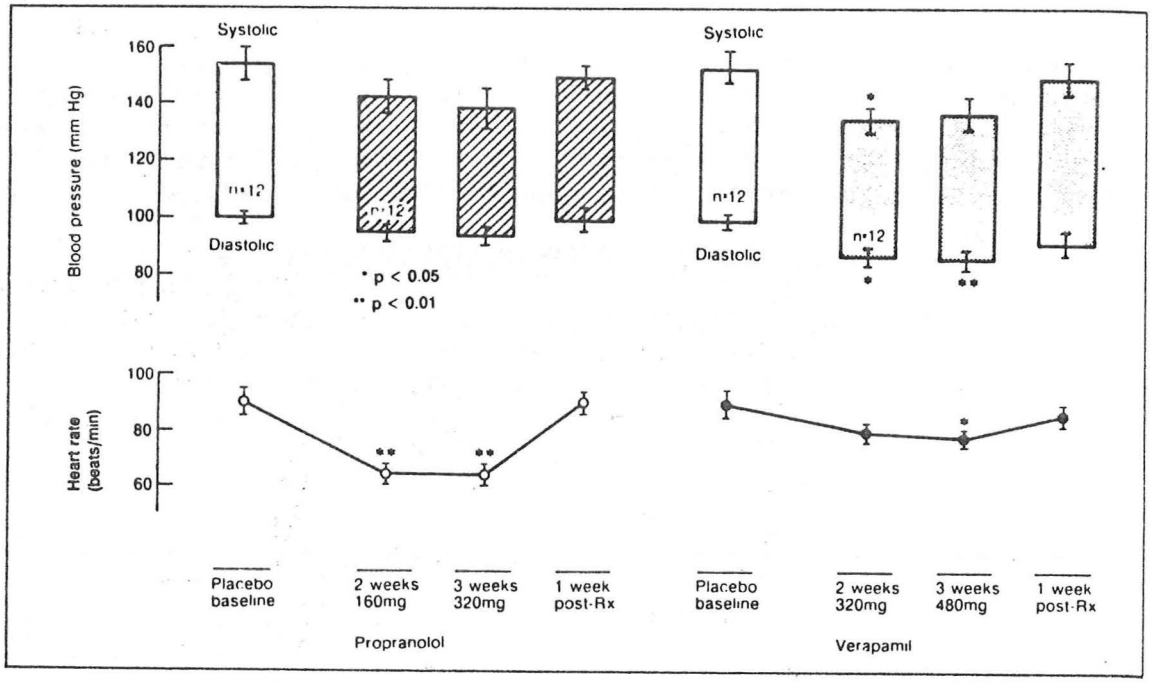


Figure 22: Standing blood pressure (BP) and heart rate at rest before, during and after treatment with increasing doses of oral propranolol and verapamil. Comparisons are made with placebo baseline, values are mean±SEM; p = probability; Rx = treatment. From Frishman et al 1982.

A number of metabolic parameters -hypercalcemia, hyperuricemia, hypokalemia, etc.- were reversed when verapamil was substituted for hydrochlorothaizide in a group of hypertensive patients (Lehtonen and Gordin 1984). If these observations are confirmed by further experience, verapamail may be an alternative to diuretics in monotherapy of hypertension.

Verapamil in Combination with Other Drugs

The addition of verapamil to a group of hypertensive patients who were already on thiazides, methyldopa or clonidine resulted in improved blood pressure control (Lewis 1980). No major untoward reactions were reported. There is no systematic experience with verapamil in combination with other hypotensive agents. The combination of verapamil with beta-blockers has to be used with considerable caution because of their shared negative effects on the conduction system and myocardial contractility.

Diltiazem

Compared to nifedipine and verapamil, experience with diltiazem in the treatment of hypertension is limited (Tables 12 and 13). Emerging reports suggest that diltiazem effectively lowers the blood pressure in hypertensive individuals (Yamakado et al 1983, Klein et al 1983, Maeda et al 1981, Aoki et al 1983) (Figures 23 and 24). During a four month treatment period, diltiazem alone or in combination with a diuretic produced significant blood pressure reduction without inducing tachycardia (Meada et al 1981). In a comparative study, the effects of diltiazem (180

mg/day) and nifedipine (30 mg/day) on the blood pressure and vascular resistance were similar (Klein et al 1983). In contrast to nifedipine, however, diltiazem did not cause reflex activation of the sympathetic tone. The absence of tachycardia with diltiazem despite the vasodilation may be due to its direct action on the sinus node (Briley et al 1980).

Table 12: DILTIAZEM IN HYPERTENSION

- Monotherapy
- Comparison with other antihypertensive drugs

Table 13

SHORT TERM DILTIAZEM MONOTHERAPY

Study (Ref)	No. Patients	Maximal Oral Dose (mg/day)	Duration of Therapy (wks)	Average Supine Blood Pressure (mm Hg) Pretreatment	Post Treatment	Decline in Blood Pressure (mm Hg)
Klein et al 1983	23	270	8	152/105	143/94	9/11
Safar et al 1983	11	--	-	179/90	165/81	14/9
Levenson et al 1983	16	--	-	181/90	157/84	24/6

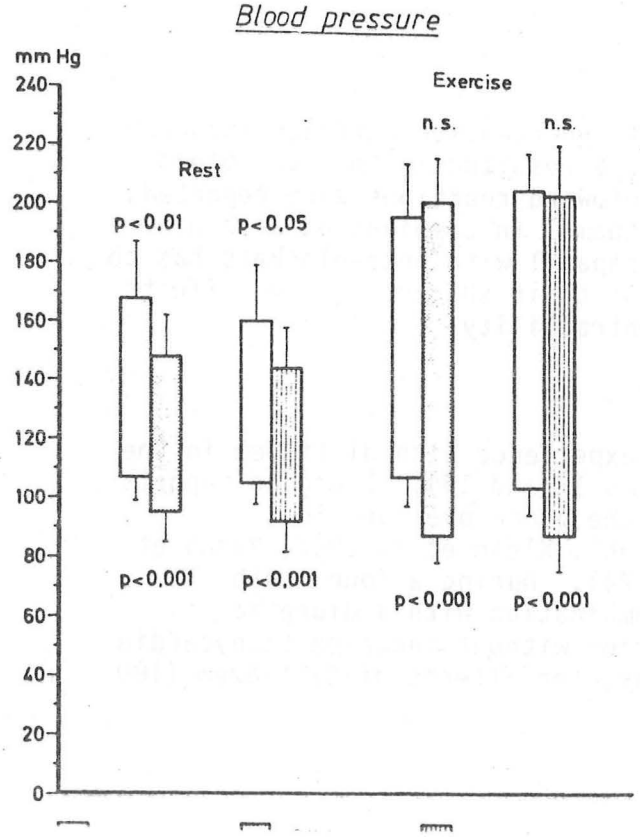


Figure 23: Resting and working blood pressure before and after 8 weeks of therapy with nifedipine or diltiazem. From Klein et al 1983.

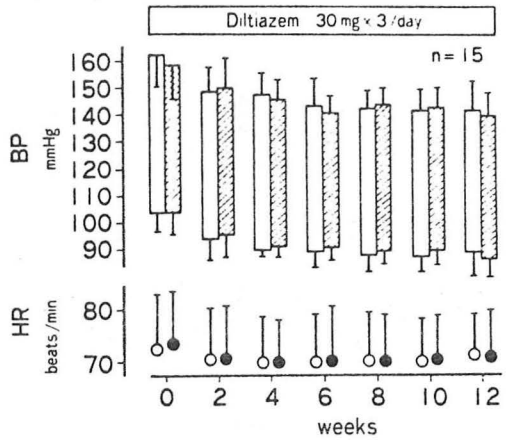


Figure 24: Blood pressure (BP) and heart rate (HR) in Group 5 patients in the supine ( ) and sitting ( ) positions during treatment with diltiazem. m±SD. From Aoki et al 1983.

The hypotensive effect of diltiazem both acutely and in the long term (18 weeks) was studied in 55 patients with essential hypertension and in 8 normotensive persons (Aoki et al 1983). The results indicate that diltiazem causes a significant blood pressure reduction in the hypertensives but not in the normotensives further lending support to the hypothesis that calcium metabolism in the vascular smooth muscle may be altered in hypertension. The hemodynamic response to diltiazem in hypertension is not fully understood and probably depends on the state of myocardial function. Acutely, diltiazem may induce a modest increase in the heart rate but during long term administration, heart rate may actually decrease (Aoki et al 1983, Yamakado et al 1983) or does not change (Inouye et al 1984). Compared to hydralazine, diltiazem did not change the heart rate despite equivalent vasodilation and an increase in the arterial diameter (Levensen et al 1983).

Comparative clinical studies have shown that the efficacy of diltiazem in hypertension is equal to that of hydrochlorothiazide (Inouye et al 1984) (Figure 25), propranolol (Yamakado et al 1983), metoprolol (Trimarco et al 1984), and nifedipine (Klein et al 1983). Diltiazem reduced the blood pressure even during exercise and this property may have clinical benefits (Yamakado et al 1983). In renal hypertension, the effectiveness of diltiazem was not maintained during long term use (Sakuri et al 1972). Clearly, more studies are needed to confirm the usefulness of diltiazem in hypertension.

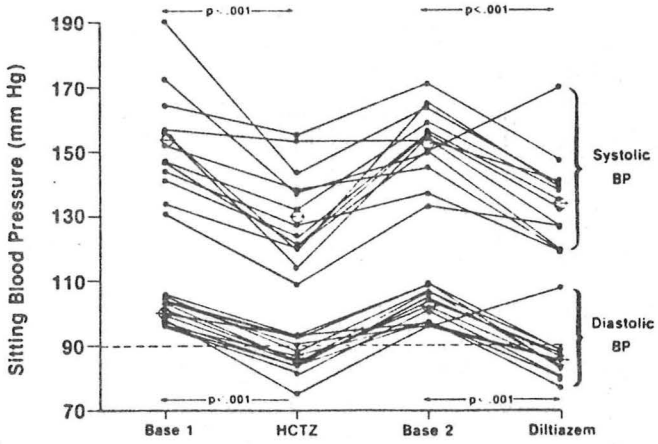


Figure 25: The effects of hydrochlorothiazide (HCTZ) and diltiazem on sitting systolic and diastolic blood pressure (BP) in individual subjects. The means for the 2 baselines are almost identical and both drugs significantly lowered systolic and diastolic BP by similar amounts. Four patients receiving HCTZ did not achieve the therapeutic goal of a diastolic pressure below 90 mm Hg (indicated by interrupted line). compared with 1 treatment failure with diltiazem therapy. The patient in whom diltiazem therapy failed had a paradoxical increase in pressure. From Inouye et al 1984.

Comparative Antihypertensive Effects of Nifedipine, Verapamil, and Diltiazem

Nifedipine is the most potent vasodilator of the three calcium antagonists. The acute effects of nifedipine are more pronounced than those obtained with verapamil and diltiazem. Nifedipine is also suitable for the management of severe, uncontrolled hypertension. Clearly, it is an attractive choice for the management of hypertensive crises where it offers the advantages of convenience, ease of administration, and effectiveness. The use of nifedipine in the acute and chronic phases may be associated with reflex tachycardia necessitating co-administration of a beta-blocking drug. Nifedipine is not known to inhibit A-V conduction.

Table 14: Hemodynamic Effects of Calcium Blockers

	Diltiazem	Nifedipine	Verapamil
Coronary Vasodilatation[a]	+ + +	+ + +	+ +
Peripheral Vasodilatation[a]	+	+ + +	+ +
Heart Rate	↓	reflex ↑	↑ or ↓
LV Contractility	–	– or reflex ↑	↑ or ↓
A-V Nodal Conduction	↓	–	↓ ↓

[a]Symbols represent the magnitude of the indicated effect induced by each agent (where + < + + < + + +). ↑ - increase; ↓ - decrease; ↓ ↓ -large decrease: – - no effect.

Table 15: CONSIDERATIONS IN THE CHOICE OF A CALCIUM ANTAGONIST

- Severity of hypertension

- Need for urgent blood pressure reduction

- Cardiac status - contractility, conduction

- Co-existing conditions, e.g. peripheral vascular disease

- Concomitant drug therapy, e.g. - a beta blocker

Verapamil produces satisfactory blood pressure reduction and does not cause tachycardia. It may be useful as initial monotherapy in hypertension, as an alternative to a diuretic or a beta-blocker. It has also been shown that in uncomplicated hypertension, verapamil may be as effective as nifedipine (Midtbo et al 1982) (Figure 26A). Preliminary experience indicates that verapamil may be particulary effective in the elderly and in the low-renin patients. The drug should be used with caution if at all in patients with impaired conduction or myocardial function.

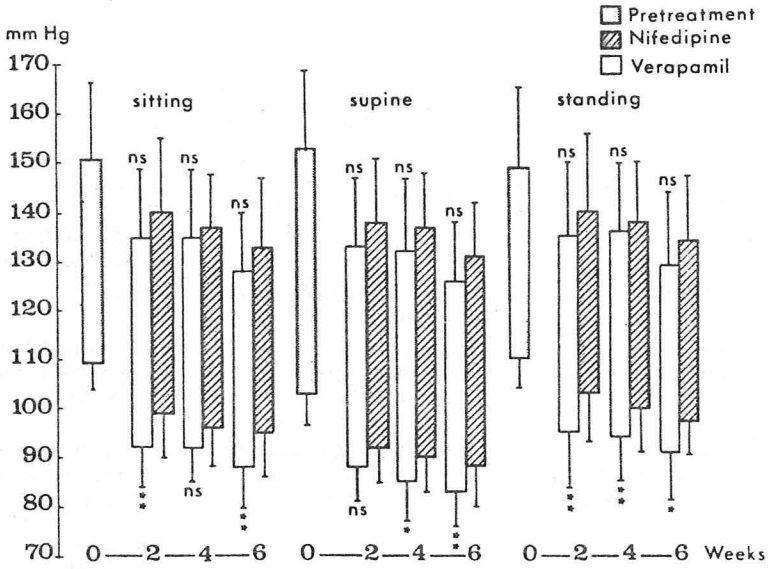


Figure 26A: Mean systolic and diastolic blood pressure in patients in the sitting, supine, and standing positions before treatment and after 2,4, and 6 weeks of treatment with verapamil and with nifedipine. The indication of significance (ns, not significant; *,$p < 0.05$; ** $p < 0.01$) refers to the mean differences between verapamil and nifedpine. From Midtbo et al 1982.

Experience with diltiazem in hypertension is not as extensive as with nifedipine or verapamil but it may very well be useful as initial therapy in hypertension. Its effects on blood pressure are similar to those of propranolol, metoprolol, or hydrochlorothiazide. However, further experience is in order to clarify the potential role of diltiazem in the management of hypertension.

It is too soon to say whether calcium antagonists will ultimately be better than other antihypertensive drugs. A number of advantages conferred

by calcium antagonists suggest that treatment with these compounds reduces the blood pressure and improves the blood flow to the tissues. The place of calcium antagonists in the anti-hypertensive drug armamentarium will depend on the results of long term treatment in comparison with other drugs, especially beta-blockers and on the assessment of patients quality of life as reflected by adherence to treatment, adverse effects, reduction in coronary mortality and preservation of tissue flow and function.

Pharmacokinetic and Pharmacologic Features of Calcium Antagonists

The pharmacokinetic characteristics of calcium antagonists are now becoming available in detail because of improved analytical techniques. In the United States nifedipine is presently available only in the liquid-filled capsule form; in other countries both the capsule and tablet form are available. Nifedipine is well absorbed after oral or sublingual administration (McAllister et al 1985) (Table 16). Nifedipine is extensively protein-bound. Elimination half-life of nifedipine has been reported to be about 4-5 hours (Stone et al 1980). Only about 20 to 30% of nifedipine is removed by the liver yielding a systemic bioavailability of more than 65%.

Table 16

Pharmacologic Features of Calcium Channel Blockers

	Nifedipine	*Diltiazem*	*Verapamil*
Available form	10-mg capsules	30- and 60-mg tablets	Injectable solution 80- and 120-mg tablets
Average half-life	4-5 hours	3-4 hours (wide individual variation)	3-7 hours
Metabolism, metabolite activity, excretion	Hepatic metabolism, inactive metabolites, 80% renal excretion	Hepatic metabolism, metabolites partially active, 70% gastrointestinal excretion	Hepatic metabolism, active metabolites, 70% renal excretion
Dosage	Initial: 10 mg 3 or 4 times daily Maximum: 120-180 mg/day	Initial: 30 mg 4 times daily Maximum: 240 mg/day (possibly higher)	IV: Bolus of 0.15 mg/kg (average in adults: 5-10 mg); maintenance infusion of 0.005 mg/kg/min Initial: 80 mg 3 or 4 times daily Maximum: 480 mg/day

Although verapamil is well absorbed after oral administration, its bioavailability is low (20%) because of extensive first-pass hepatic metabolism. In patients with hepatic cirrhosis, clearance of verapamil is decreased enhancing its bioavailability (McAllister et al 1985). In patients with cirrhosis, the dosage of verapamil has to be decreased. The half-life of verapmail during chronic administration increases due to reduced first-pass metabolism. Therefore stable plasma concentrations of verapamil might be achieved with an 8-hourly or even a 12-hourly schedule with chronic use (Freedman et al 1982).

Diltiazem is rapidly and nearly completely absorbed. Like verapmail,

diltiazem undergoes considerable hepatic extraction reducing its biovavilability to 24% (Peipho et al 1982). During long term administration, bioavailability of diltiazem increases due to saturation of metabolic elimination pathway (Smith et al 1983). The half-life of diltiazem is 3.1 to 3.4 hours. Although specific information is lacking, it is probably necessary to modify the dosage in patients with hepatic dysfunction as is the case for verapamil.

Electrophysiological Effects of Calcium Antagonists

In clinically relevant concentrations, none of the calcium antagonists affect the electrophysiological features of the atrial or ventricular muscle. The most notable electrophysiological effects of calcium antagonists are on the A-V conduction. Nifedipine may facilitate, not suppress A-V conduction. Any negative effect of nifedipine on A-V nodal conduction is weak and is overcome by reflex increases in the sympathetic tone (Narimatsu and Taira 1976, Ellordt and Singh 1983). In clinical settings, nifedipine does not affect A-H and H-S intervals of HIS-bundle electrograms. The lack of any significant electrophysiological properties, particulary on the conduction system explains the lack of anti-arrhythmic activity of the drug (Padeletti et al 1980, Fujimoto et al 1981). Thus, in combination with beta-blockers and digoxin, nifedipine is less hazardous than is verapamil.

The electrophysiological effects of verapamil are more pronounced in the conduction system. Verapamil depresses the SA nodal and AV conduction activity (Ellordt and Singh 1983) - these effects form the basis for the use of this drug in supraventricular tachyarrhythmias. The electrophysiological effects of diltiazem are more akin to those of verapamil than those of nifedipine (Saini 1984) - like verapamil, diltiazem suppresses A-V nodal conduction and prolongs refractory periods (Table 17).

Table 17: Differential effects of verapamil, nifedipine and diltiazem

Action	Verapamil	Nifedipine	Diltiazem
Effect on fast channels	+	0	+
Local anaesthetic effect	+	0	+
Slowing of AV conduction	+	0	+
Prolongation of refractory period in AV node	+	0	+
Vascular O_2 consumption	↓	0	↑
Negative inotropic/negative chronotropic effect	> 1	⩾1	< 1
Peripheral vasodilator effect	+	++	+
Activation of baroreceptor reflexes	+	++	+

All the calcium antagonists have important hemodynamic effects in man. However, these is considerable variability between agents as to their relative potensies for differenct action. Overall effects can be explained

on the basis of the inhibitory actions of these drugs on the myocardium and peripheral vascular resistance combined with the relative activation of reflex sympathetic tone. It should be remembered that the net hemodynamic effect of these compounds varies in patients with impaired myocardial contractility, myocardail infarction, or concomitant beta-blockade.

Verapamil and to some extent nifedipine exert more negative inotropic effects than diltiazem. In otherwise healthy hearts, this negative inotropic effect is not demonstrable clinically owing to reflex sympathetic response to vasodilation produced by these drugs (Millard et al 1983, Nayler and Horowitz 1983). However, the negative inotropic effects become manifest in circumstances where cardiac contractility is already decreased due to a disease or due to concurrent drug therapy. All the major calcium antagonists increase coronary blood flow both by direct smooth muscle relaxation and by secondary effects induced by reduction in myocardial oxygen demand via negative inotropic and peripheral vasodilatory actions.

Nifedipine is the most powerful peripheral vasodilator followed by verapamil and diltiazem. Nifedipine induced reduction in peripheral vascular resistance is accompanied by an increase in the heart rate and cardiac output. Verapamil too causes significant peripheral vasodilation but only a slight increase in cardiac output; tachycardia is not seen due to its negative inotropic actions. Diltiazem has very little effect on myocardial function and produces no reflex changes in the sympathetic tone.

In summary, with nifedipine one is likely to see potent coronary and system vasodilation accompanied by enhanced cardiac output and no change in the conduction. With verapamil, one can expect moderate vasodilation and no tachycardia. Similar effects are seen with diltiazem. The net hemodynamic outcome in a given patient depends on the variable myocardial depressant, vasodilatory, and reflex responses (Table 18) (Figure 26B).

Table 18: DETERMINANTS OF HEMODYNAMIC RESPONSE TO CALCIUM ANTAGONISTS

1. Effect on Myocardium
2. AV Conduction
3. Peripheral Vasodilation
4. Coronary Blood Flow

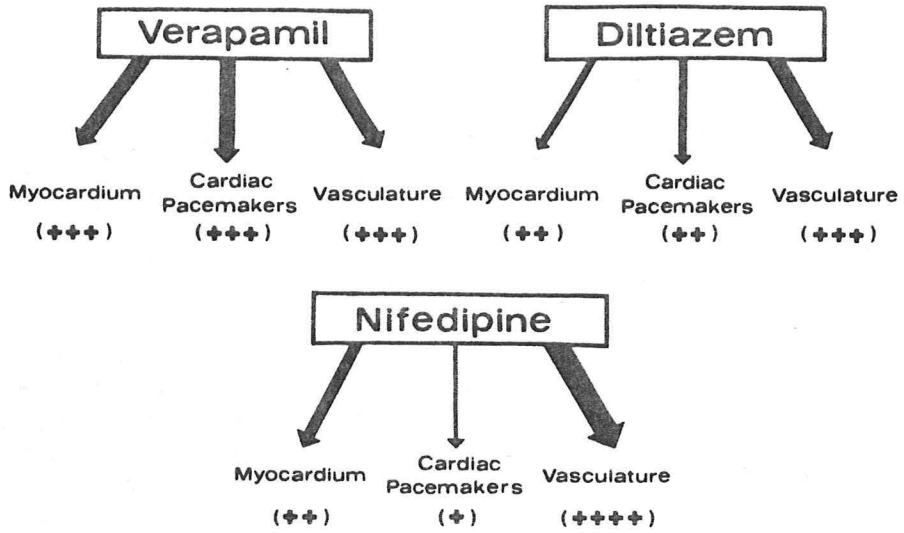


Figure 26B: Potential inhibitory effects of therapeutic doses of Ca antagonists on myocardial contractility, SA-node automaticity, and AV conduction as well as vascular smooth muscle tone and spasms, particularly in coronary stem arteries. However, these potential negative inotropic, chronotropic, and dromotropic actions of systemically administered Ca antagonists are usually subject to considerable attenuation by sympathetic cardiovascular reflexes. Conversely, baroreceptor-mediated increases in sympathetic drive contribute additionally to extramural coronary vasodilation.

Dosage: For the acute control of hypertension on an urgent basis, nifedipine should be administered sublingually or orally as 10 mg dose. If no response is seen a second dose can be given in 2-3 hours although one can argue that if the first dose fails to show a response, a second dose can ge given much sooner.

For the chronic management of hypertension, dosage schedules are similar to those used in the treatment of coronary artery disease/supraventricular arrhythmias (Table 16). There is great variability in the duration of action of these drugs and with chronic dosing the frequency of administration can be reduced. Certainly, when available for routine use the long acting preparations of nifedipine and verapamil should help simplify the schedule.

Drug Interactions

Table 19: DRUG INTERACTIONS OF CALCIUM ANTAGONISTS

1. With beta-adrenergic blockers
2. With digoxin
3. With other drugs - quinidine, histamine$_2$ antagonists

Nifedipine and Beta-blockers

Since nifedipine causes reflex activation of the sympathetic tone, co-administration of a beta-blocking drug is beneficial (Aoki et al 1978). In properly selected patients, side effects from nifedipine-beta-blocker interaction can be expected to be minimal. In a review of 1400 patients receiving this combination, the incidence of adverse effects was no greater than with nifedipine alone (Terry 1982). It must be emphasized, however, that the major hemodynamic effect of nifedipine is via reflex adrenergic mechanism and when this is blocked, the drug may exert a significant negative inotropic effect (Figure 27A). On combined nifedipine and propranolol therapy, reports of heart failure (Nakamoto 1975, Anastassiados 1980) and hypotension (Opie and White 1980, Aoki et al 1978, Staffurth and Emery 1981) have occasionally appeared. Although the nifedipine-beta-blocker combination is generally safe, patients should be monitored for any possible adverse effects.

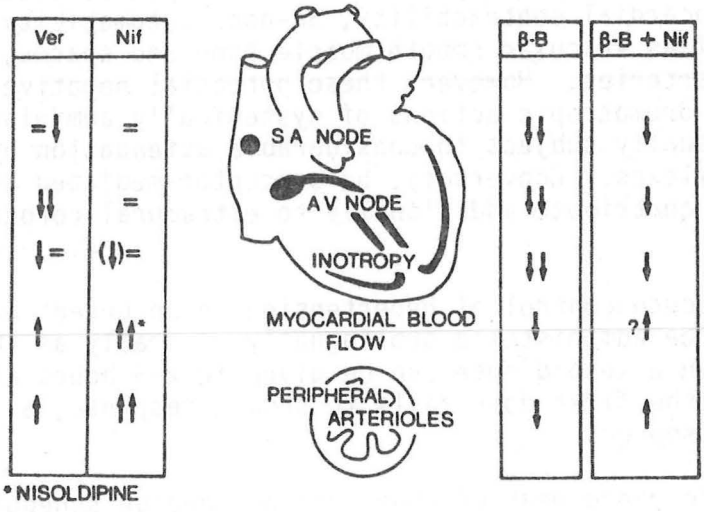


Figure 27A: Effect of Ca^{2+} antagonists and beta-blockade alone and in combination on cardiovascular system. Ver, verapamil; Nif, nifedipine.

Nifedipine and Digoxin: A kinetic interaction between digoxin and nifedipine resulting in increased plasma digoxin level was reported (Belz et al 1982) but this was not confirmed in other studies (Kuhlmann 1985, Schwartz et al 1984, Schwartz and Migliore 1984). The reason for this discordance is not clear and nifedipine can be safely administered to patients on digoxin therapy.

Nifedipine and H_2 Antagonists: Increased plasma levels of nifedipine have been reported in patients receiving cimetidine or ranitidine (Kirch et al 1982). How significant this can be clinically is not known. Since cimetidine decreases hepatic blood flow and hepatic microsomal enzyme activity and ranitidine decreases hepatic blood flow, plasma nifedipine levels may increase due to a kinetic interation with these drugs. Whether this potential interaction augments the hypotensive effects of nifedipine remains to be seen.

Verapamil and Beta-Blockers: The potentially dangerous consequences of combining verapamil and beta-blockers have received the most publicity. Bradycardia, prolonged hypotension, A-V block, and ventricular asystole have been reported following intravenous administration of verapamil to patients receiving beta-blockers (Waxman et al 1981, Boothby et al 1972, Singh et al 1979). A subsequent study examined the effects of chronic oral administration of verapamil and propranolol (Subramanian et al 1982); in this study 9 of 40 patients treated chronically showed cardiac decompensation. The relative safety of propranolol-verapamil in patients with well preserved ventricular function has been documented (Kieval et al 1982, Packer et al 1982). However, combined verapamil-beta-blocker is risky in patients with impaired ventricular function and AV conduction where their additive effects may be diastrous.

Verapamil and Digoxin: Verapamil has been shown to decrease renal clearance and increase the plasma levels of digoxin (Belz et al 1981, Klein et al 1982). The magnitude of increase in the serum digoxin concentrations induced by verapamil is dictated by the dose of the latter and may be up to 100% (Klein et al 1982). The frequency of overt digoxin toxicity due to concomitant verapamil therapy is unpredictable. Thus, caution and monitoring is advised whenever verapamil and digoxin are given together.

Diltiazem and Beta-Blockers: Whereas while diltiazem appears to have very little negative inotropic activity, its electrophysiological actions are similar to those of verapamil; caution must be exercised when using it along with beta-blockers.

Diltaizem and Digoxin: While experience with diltiazem-digoxin interaction is rather limited, preliminary experience suggests that serum digoxin levels are increased by diltiazem (Rameis et al 1984, Kuhlamann 1985).

Adverse Effects

The expected adverse effects of calcium antagonists are related to their vasodilatory and cardiac actions. The type and extent of an adverse effect depend on the route of administration, dosage, and cardiac status of the patient. Adverse reactions may result from the drug's known pharmacological actions, from altered pharmacokinetics, and from interaction with other drugs. Due to their chemical heterogeneity and preferential effects on tissues, adverse reactions from different calcium antagonists vary (Lewis 1983, Krebs 1983) (Table 20). As with most cardiovascular drugs, the risk is enhanced when the heart is damaged.

Table 20: Adverse Side Effects

	Diltiazem	Nifedipine	Verapamil
Overall frequency[a]	~4%	~17%	~9%
Intolerable[a]	0%	5%	1%
Hypotension	−	+ + +	+
Dizziness/Headaches[b]	+	+ + +	+ +
Peripheral Edema[b]	±	+ +	±
Constipation[b]	−	−	+ +
A-V Block[b]	±	−	+
Heart Failure[b]	−	−	+

[a]Values represent % of patient population receiving indicated therapy and reporting adverse side effects which are believed to be due to the indicated medication.
[b]Symbols represent relative frequency of indicated adverse side effect ranging from lowest (non existent) (−) to highest (+ + +) (− < ± < + < + + < + + +).

Nifedipine: The important adverse effects of nifedipine are attributable to vasodilation. Some patients report headache, flushing, and palpitations. The last effect is minimized by a beta-blocker. An annoying effect of nifedipine is ankle edema which is not due to generalized fluid retention or weight gain. It may not respond to diuretics but clears when the drug is withdrawn. The ankle edema is presumably due to local pre-capillary (without postcapillary) dilation which increases the filtration pressure and causes transudation of fluid.

A recent review of the clinical course of 3000 patients treated with nifedipine gives useful information (Terry 1982). Dizziness was reported in 21.1%, edema in 7.7%, headache in 7%, flushing in 7%. It is interesting to note that hypotension, heart failure occurred in < 4% of patients. Aggravation of myocardial ischemia has been reported in some patients (Boden et al 1985). Occasionally acute treatment of hypertension with nifedipine may result in severe hypotension (Heidland et al 1982), and ischemic ECG changes (Yagil et al 1982). Rarely cerebral ischemia has been reported to occur following nifedipine therapy (Nobile-Orazio and Sterzi, 1981). Rather a peculiar side-effect - gingival hyperplasia - attributable to nifedipine has been reported in 5 patients (Ramon et al 1984). The morphology and histology of this lesion are reminiscent of diphenylhydantoin induced gingival hyperplasia. Whether this adverse effect is unique to nifedipine or is due to calcium antagonism is unknown. Since dilantin and nifedipine share the capacity to alter calcium metabolism, one wonders about the common basis for this reaction.

Verapamil: The major reported adverse effects of verapamil have been the hemodynamic disturbances following intravenous administration. Clinically significant hemodynamic deterioration is rare during chronic oral verapamil therapy. Constipation is probably the most common side effect of verapamil therapy (Nayler and Horowitz 1983). Other adverse effects include gastric irritation, vertigo, headache and ankle edema. In general, these side effects are mild and can be managed conservatively. Prolongation of AV block occurs in some patients due to chronic oral therapy. But in the absence of underlying conduction system disorder, advanced degrees of heart block are unusual. In patients with normal ventricular function, precipitation of CHF by verapamil is quite unusual. In the presence of CHF, however, verapamil should be used with great caution or not at all. Severe hypotension and AV block associated with overdose of verapamil can be successfully reversed with calcium gluconate infusion (Woie and Storstein, 1981).

Diltiazem

Experience with diltiazem associated adverse effects is limited. Overall, diltiazem appears to have the lowest incidence of side effects among the currently available calcium antagonists (Ellrodt and Singh 1983). In 63 patients, the incidence of adverse effects during diltiazem or placebo treatment was similar (Strauss et al 1982). Dizziness, headache, flushing appear only rarely. Diltiazem must be used with caution in patients with impaired left ventricular function or conduction disturbances.

Calcium Antagonists and Renal Function

The effects of calcium antagonism on renal function have not been studied extensively and with their increasing use, it will be important to know if calcium antagonists have any direct renal efects. There are sketchy largely uncontrolled studies which indicate that calcium antagonists may cause natriuresis (Van Schaik et al 1984, Christensen et al 1982, Leonetti et al 1980, Garthoff ef al 1983). Although the mechanism of enhanced sodium excretion with calcium antagonists is not known, it was demonstrated that nitrendipine increased sodium excretion without an effect on aldosterone secretion (Sambhi et al 1984), suggesting a possible direct tubular effect. Diltiazem appears to increase GFR and cause natriuresis despite a decrease in the blood pressure (Kinoshita et al 1978). More carefully designed, controlled studies should be done to determine the effect of calcium antagonists on the renal function. A uricosuric effect was observed in one study (Christensen et al 1982) (Figure 27B).

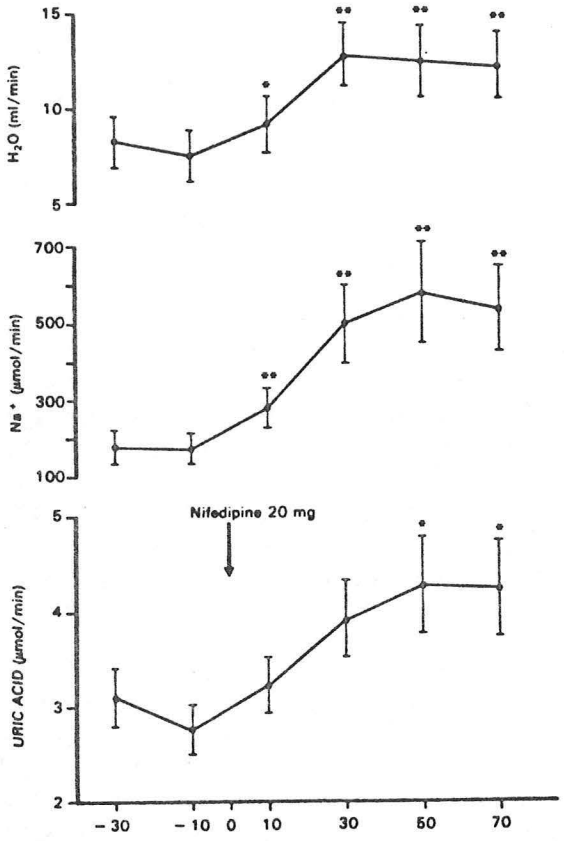


Figure 27B: Urinary excretion rate of water, sodium and uric acid before and after the acute administration of nifedipine 20 mg in hypertensive patients on long-term beta-blocker therapy. (Christensen, Lederballe Pedersen & Mikkelsen 1982).

Therapy with nifedipine in hypertensive patients with chronic renal failure yielded satisfactory effects without any drug related adverse effects (Kusano et al 1984, Kubo et al 1983). The safety of calcium antagonists in patients with underlying renal disease is not known. Until then, the use of these drugs in renal insufficiency must be dictated by the therapeutic need and benefit:risk assessment in individual patients. In a retrospective study, nifedipine therapy was associated with deterioration in renal function in four patients with pre-existing renal failure (Diamond et al 1984).

Humoral and Metabolic Effects of Calcium Antagonists

It is clearly established that Ca^{2+} plays a major role in coupling certain extracellular signals to the appropriate physiological response of a cell and various secretory processes. Agents that prevent the penetration of Ca^{2+} into intracellular space may interfere with stimulus-secretion coupling (Fleckenstein 1977). Agents such as verapamil and D-600 (Methoxyverapamil) have been experimentally utilized to probe the dependence on Ca++ uptake of hormone secretion from pituitary (Eto et al 1974) isolated pancreatic cells (Devis et al 1975) and hormone producing tumor cells (Erlichman et al 1979). Secretion of at least some hormones is dependent on calcium transport across the cell membrane (Millar and Struthers, 1984). Calcium is not only necessary for synthesis of certain hormones but their release (by exocytosis or other mechanisms) may be calcium dependent. Thus at least theoretically, calcium antagonists can influence hormonal release under experimental conditions but the clinical relevance of such largely in vitro observations is uncertain. Furthermore acute humoral responses to calcium antagonists may be quite different from those seen during chronic treatment and considerable caution must prevail in interpreting the published reports.

Acutely, nifedipine increases plasma renin activity (PRA) and catecholamines but the initial rise in sympathetic activity decreases during prolonged therapy (Lederballe-Pedersen et al 1979). This observation raises the speculation whether co-administration of a beta-blocker is necessary during chronic therapy to block the reflex activation of the sympathetic tone. Nifedipine causes a greater increase in the plasma catecholamines compared to verapamil (Muiesan et al 1982) (Table 21). The effect of nifedipine on PRA and catecholamines depends on the hemodynamic response, acute or chronic administration, and is therefore quite variable.

Table 21: Results of controlled study before and after 8 days of verapamil or nifedipine treatment. (From Muiesan et al 1982).

	Basal		Verapamil (80 mg t.i.d.)		Nifedipine (10 mg t.i.d.)	
	Supine	Standing	Supine	Standing	Supine	Standing
SAP (mm Hg)	164 ± 15	161 ± 14	141 ± 8[a]	138 ± 10[a]	138 ± 9[a]	129 ± 11[a]
DAP (mm Hg)	106 ± 10	111 ± 10	91 ± 6[a]	95 ± 5[a]	90 ± 9[a]	88 ± 10[a]
HR (b/min)	74 ± 6	84 ± 8	74 ± 12	81 ± 13	76 ± 15	96 ± 8[b]
NE (ng/L)	156 ± 45	311 ± 120	194 ± 80	352 ± 164	297 ± 158[b]	500 ± 243[c]
E (ng/L)	69 ± 44	86 ± 47	82 ± 35	90 ± 58	92 ± 40	185 ± 149[c]
PRA (ng/ml/h)	1.6 ± 1.5	3.7 ± 3.4	1.2 ± 1.3	3.0 ± 2.8	2.5 ± 1.4	4.2 ± 2.1
ALD (ng/L)	92 ± 54	203 ± 98	95 ± 92	145 ± 83	64 ± 20	128 ± 85
PV (ml/cm)	18.9 ± 2.8		19.2 ± 3.4		19.4 ± 2.5	
BW (kg)		71.3 ± 6.5		70.8 ± 8.2		70.4 ± 6.6

Systolic and diastolic arterial pressure (SAP, DAP), HR, plasma NE and E, PRA, plasma ALD, PV, and body weight (BW) were measured.

Data are mean ± SD. Significance of differences is calculated with respect to basal values: [a] $p < 0.01$, [b] $p < 0.01$; [c] $p < 0.05$.

The effect of acute administration of nifedipine on adrenocortical responses to trophic stimuli was studied in patients with essentail hypertension and in normals (Millar et al 1982); the findings indicate that aldosterone response to angiotensin infusion was decreased whereas the responsiveness to ACTH was preserved implying that nifedipine may decrease the zona glomerulosa senstivity to angiotensin but has no effect on ACTH stimulated aldosterone mechanism. Ca++ antagonism may have a selective effect on the adrenal gland; for example it was shown that nifedipine stimulates renin release which is not accompanied by enhanced aldosterone secretion (Pedersen et al 1979) (Figure 28). This finding if further substantiated may have practical implications relative to potassium homeostasis during nifedipine therapy.

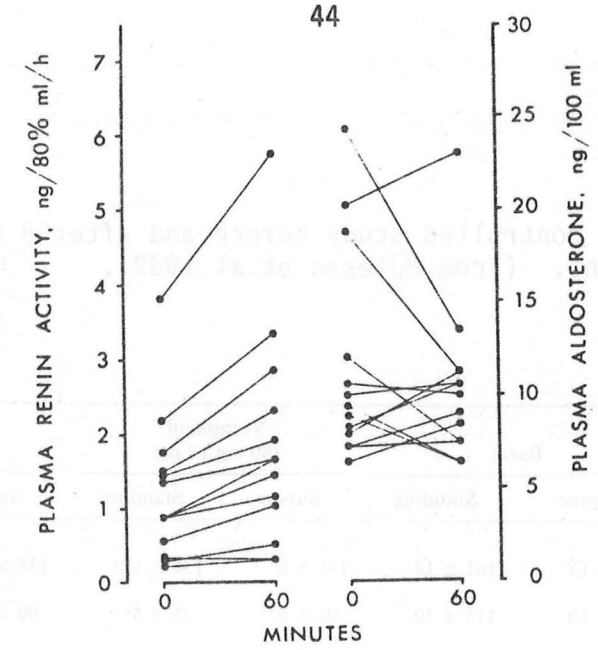


Figure 28: Plasma renin activity (left) and aldosterone concentration (right) before and 60 min after sublingual administration of nifedipine 10 or 20 mg to 13 patients with essential hypertension. From Pendersen OL et al 1979.

The aldosterone and pressor responsiveness to angiotensin II infusion is blunted by nifedipine therapy in normal individuals (Millar et al 1981) (Figure 29) suggesting that transmembrane movement of calcium is involved in aldosterone response to angiotensin II. The relative contribution of this phenomenon to the overall anti-hypertensive effect of nifedipine is unclear.

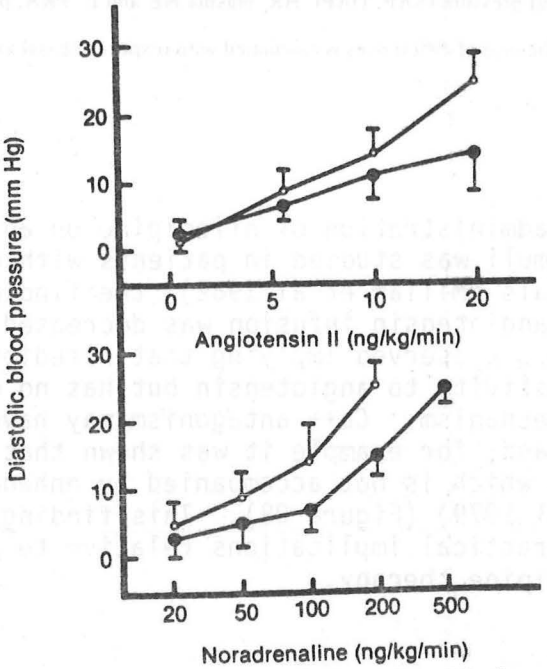


Figure 29: Pressor responses to angiotensin II (upper panel) and noradrenaline (lower panel) after three days of treatment with nifedipine (•——•) or placebo (o——o) in six normal subjects. Responses were determined on the morning of the fourth day of treatment, one hour after nifedipine or placebo administration. From Millar et al 1981.

It is interesting to note that nifedipine therapy normalized the blood pressure and plasma aldosterone levels in 5 patients with primary aldosteronism (Nadler et al 1984). The inhibitory effect on aldosterone may explain natriuresis that has been noted with nifedipine (Christensen et al 1982). Nitrendipine however was noted to increase urinary excretion of sodium without an effect on aldosterone suggesting a direct natriuretic effect of this drug in man (Sambhi et al 1984) and in the Dahl-Srats (Garthoff et al 1983) (Figure 30).

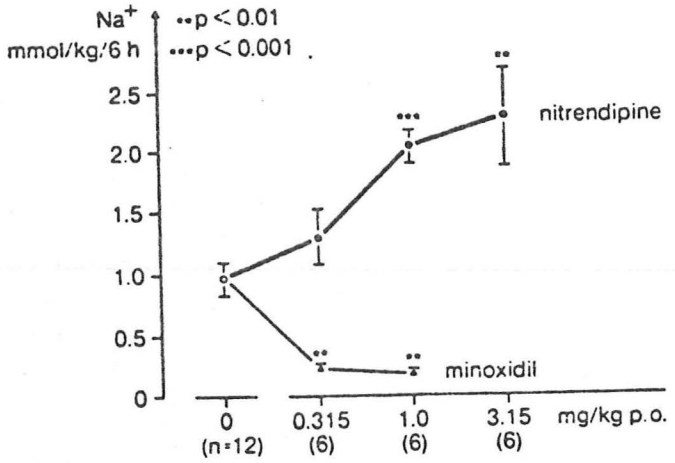


Figure 30: Natriuresis in Dahl-S rats after saline load during treatment with calcium antagonist (nitrendipine), or minoxidil. From Garthoff et al 1983.

Glucose stimulation of insulin secretion can be prevented by elimination of extracellular Ca^{2+} or by the addition of Ca^{2+} antagonists; verapamil induced inhibition of insulin release can be partially overcome by increasing the extracellular Ca++ (Fleischer et al 1981, Devis et al 1975). The clinical implications of this in normal, hypertensive, and diabetic subjects is unknown.

It has been suggested that in vitro TRH requires extracellular Ca++ which may serve as a second messenger to couple TRH action and hormone secretion (Tashjian et al 1978). The relevance of these in vitro findings to the in vivo situations is uncertain.

Divergent findings have been reported concerning the effects of verapamil on FSH, LH, TSH. While in one study verapamil inhibited the stimulated release of FSH, LH and TSH (Barbarino and De Marinis 1980), in another these parameters were unchanged (Semple et al 1984). These differences could be partially explained by the route of administration of the drug. Verapamil undergoes extensive first pass extraction and it is probable that high concentrations were achieved by intravenous verapamil in the Barbarino and DeMarinis study; the differences in the drug level may account for the disparate observations.

Calcium Antagonists and Glucose Metabolism

Hyperglycemia has been reported with nifedipine (Zezulka et al 1984, Charles et al 1981, Guigliano et al 1980). This effect is inconsistent and

may be related to direct inhibition of calcium antagonists on insulin secretion or due to extra-hepatic causes (DeMarinis, Barbarino 1980). In patients with insulinoma, the frequency of hypoglycemic attacks was minimized by diltiazem (Taniguchi et al 1979) and verapamil (Andersson et al 1980). Other studies revealed no changes in the insulin secretion in humans with healthy pancreas (DeMarinis and Barbarino 1980, Donneley and Harrower 1980, Segrestaa et al 1984). The full impact and clinical ramifications of the above findings in the clinical managmeent of patients with and without diabetes is unclear. Obviously blood glucose has to be checked periodically until more definitive information is available about the chronic effects of Ca++ antagonists on glucose homeostasis.

Calcium Antagonists and Effects on Bone, Calcium Metabolism: Surprisingly, despite enormous experience, little is known about the clinical effects of calcium antagonists on bone, calcium, PTH, and vitamin D metabolism. Experimentally, verapamil inhibits in vitro PTH stimulated release of calcium and phosphate (Herman-Erlee et al 1977) and reduces bone resorption caused by 1 alpha-OH-vitamin D, an effect that is reversible by either withdrawal of verapamil or by increasing the calcium concentration in the medium (Lerner and Gustafson 1982). Verapamil (again under experimental conditions) decreased skeletal collagen synthesis, but this inhibition was overcome by the addition of more calcium in the medium (Deitrich and Duffield 1979). It will be important to evaluate the significance and possible clinical implications of calcium antagonists on bone and mineral metabolism. We are currently doing a pilot study to investigate this in patients with essential hypertension.

Effects of Calcium Antagonists on The Structural Abnormalities Associated with Hypertension/Atherosclerosis

Based on preliminary data calcium antagonists may offer some advantages over the conventional antihypertensive drugs (Table 22).

Table 22: POTENTIAL ADVANTAGES OF CALCIUM ANTAGONISTS

1. Fewer significant adverse effects
2. ? Reverse the pathophysiological mechanisms) of hypertension
3. ? Regression of left ventricular hypertrophy
4. ? Suppression of atherogenesis
5. ? Inhibition of arterial calcinosis
6. Improved tissue perfusion

Left ventricular hypertrophy and dysfunction may result from untreated hypertension. The effects of current antihypertensive therapy on this structural abnormality are inconsistent. The goal of antihypertensive therapy should be to restore and preserve cardiac function in addition to blood pressure reduction. Calcium antagonists by virtue of their cellular

action may prove to be an attractive probe to investigate the possible reversal of left ventricular hypertrophy in hypertension. The premise is that increased volume load together with increased afterload contribute to left ventricular hypertrophy and calcium antagonistic drugs may prevent and or reverse cardiac hypertrophy by interruptting the underlying pathophysiological processes.

Experimentally in rats, nifedipine and nitrendipine have been shown to cause regression of cardiac hypertrophy (Kazda et al 1982, Kazda et al 1983, Motz and Strauer 1983, Kobayashi and Tarazi 1983) (Figure 31). Whether this was achieved due to blood pressure reduction or whether calcium antagonists specifically interfere with cardiac metabolism is not determined. Since other direct vasodilators like hydralazine and minoxidil do not cause regression of LVH despite adequate reduction in blood pressure, it can be speculated that calcium antagonists may have a specific favorable effect on the process of hypertrophy and its regression. It is possible that factors other than blood pressure may play a role in the genesis and reversal of LVH in hypertension. It has been argued, however, that the extent of blood pressure reduction regardless of a therapeutic regimen determines the extent of regression of structural cardiovascular changes (Lundin et al 1984). Although reversal of LVH is expected to improve left ventricular function, it does not mean that myocardial efficiency will increase (Tuban et al 1985). Clinical studies utilizing serial echocardiography during long term use of calcium antagonists should provide further insight into the influence of these drugs on the cardiac function and size. In one short-term study (1 month), nifedipine was more beneficial compared to verapamil in treatment of hypertensive heart disease (Guazzi et al 1984). This suggests that one calcium antagonist may differ from the other and the net effect depends on the influences on afterload, contractility, etc..

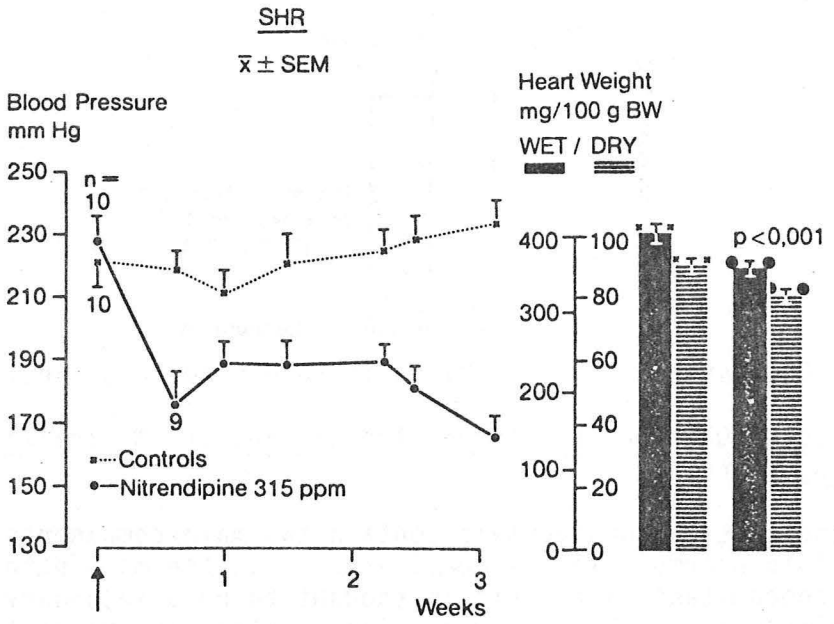


Figure 31: Effect of long-term administration of nitrendipine on the systolic blood pressure and heart weight of SHR. Adapted from Kadza et al 1983.

Influence of Calcium Antagonists on Experimental Atherogenesis

There is evidence to imply that calcium has a pathogenetic role in atherosclerosis (Blumenthal et al 1944, Kramsch et al 1981, Hollander et al 1979, Henry 1982). In cholesterol induced atherosclerosis, anticalcifying agents have anti-atherogenic effects without affecting cholesterol levels (Kramsch et al 1981, Hollander et al 1979). Since intracellular calcium accumulation may be a mediating event in hypercholesterolemic vascular lesions, studies were done to assess the effect of calcium antagonistic drugs nifedipine (Henry and Bently 1981) and verapamil (Rouleau et al 1983) on experimental atherogenesis (Figure 32). The results show that both the agents suppressed the development of atherosclerosis in rabbits fed with high cholesterol diet. These findings were not related to the blood pressure control suggesting mechanisms other than alterations in blood pressure might have accounted for the observations. Calcium overload may be a key mechanism in the proliferation of smooth muscle and cell necrosis associated with atherosclerosis. Calcium antagonists may interrupt the calcium mediated vascular injury in suppressing atherogenosis. Conflicting evidence has been presented that diltiazem and nicardipine are ineffective in suppressing the atherosclerotic process (Naito et al 1984). This raises the question whether different calcium antagonists exert disparate effects on this phenomenon. In any case, there are no clinical data to support the experimental findings and use of calcium antagonists for preventing atherosclerosis is not warranted at the present time.

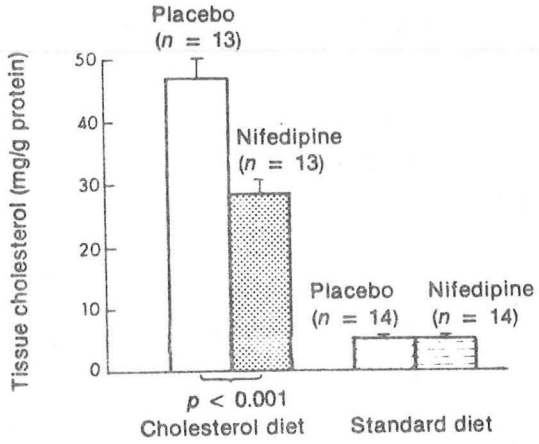


Figure 32: Cholesterol concentrations in rabbit aortas. From Henry 1982.

Vascular Calcium Overload in Atherosclerosis and Its Neutralization By Calcium Antagonists

Arteriosclerotic blood vessels contain two main components - lipids and calcium. Lipid accumulation is considered to be the main pathogenetic factor and concomitant calcinosis is thought to be a secondary event. The possible deleterious influence of calcium overload on the cellular structural and function was extensively studied by Fleckenstein's group (Fleckenstein et al 1983A, 1983B, 1984). It should be cautioned that the observations reported by Fleckenstein have not been thoroughly tested by others and application of the data to clinical practice can not be recommended at this time. Nevertheless, experimental evidence to incriminate calcium in the tissue damage and the role of calcium

antagonists in reversing this phenomenon are both intriguing and fascinating.

It has been reported many years ago that progressive calcinosis is inevitable with aging (Burger 1939). As shown in Figure 33 both the cholesterol and calcium contents of the vessel wall rise with increasing age. Ca and Mg content was analyzed on arterial walls obtained for 144 autopsies (Fleckenstein et al 1977); it was noted that progressive calcium overload correlated nicely with advanced age. It is interesting to note that the analyses were done on arterial specimens without visible plaques. Whether the steady rise in arterial Ca content is a definite risk factor for atherosclerotic process is not fully understood. Anticalcinotic effects of nifedipine were shown in the spontaneously hypertensive rat (Figure 34).

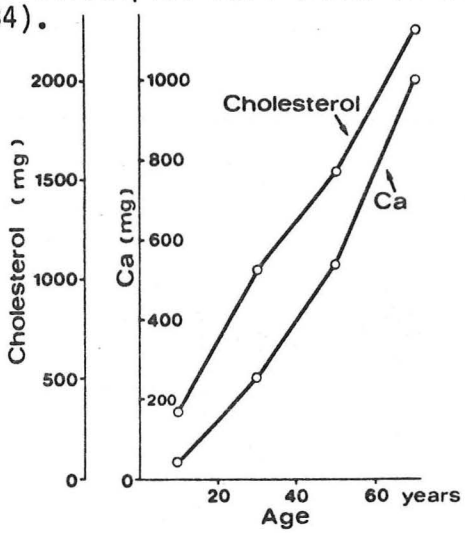


Figure 33: Age-dependent increases in Ca and cholesterol contents of the human aortic wall, expressed in mg/100 g dry tissue. From Fleckenstein A 1983B.

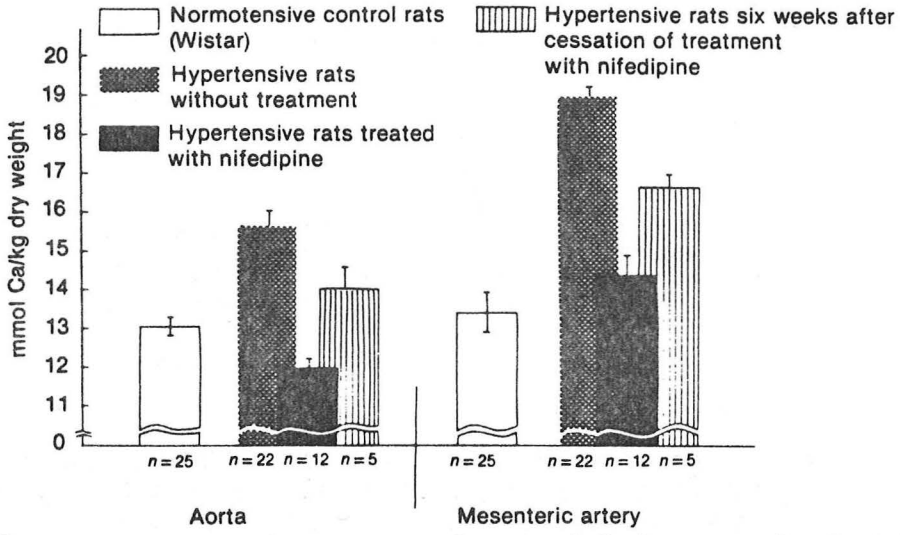


Figure 34: Recommencement of supernormal arterial Ca accumulation in spontaneously hypertensive rats after cessation of a five-month long-term treatment with nifedipine: whereas blood pressure rises within 48 hours to the level of untreated hypertensive rats, the resumption of supernormal arterial Ca uptake largely lags behind. Thus an anticalcinotic effect was still discernible six weeks after cessation of the nifedipine therapy. From Fleckenstein A 1983B.

Prophylactic actions of calcium antagonists in retarding experimentally induced arterial calcinosis were reported (Fleckenstein A 1983A). One way to produce tremendous degrees of arterial calcinosis is to give huge doses of dihydrotachysterol (DHT) and or vitamin D_3 to rats. The resultant arterial lesions are quite similar to Monckeberg's calcification in humans. Experimental calcinosis was markedly inhibited by verapamil and diltiazem (Figure 35). These observations suggest that calcium antagonists can prevent arterial calcinosis. Regardless of whether or not this hypothesis is true, the fact that calcium antagonists interfered with calcinotic process is interesting and offers an avenue for further research in artherosclerosis.

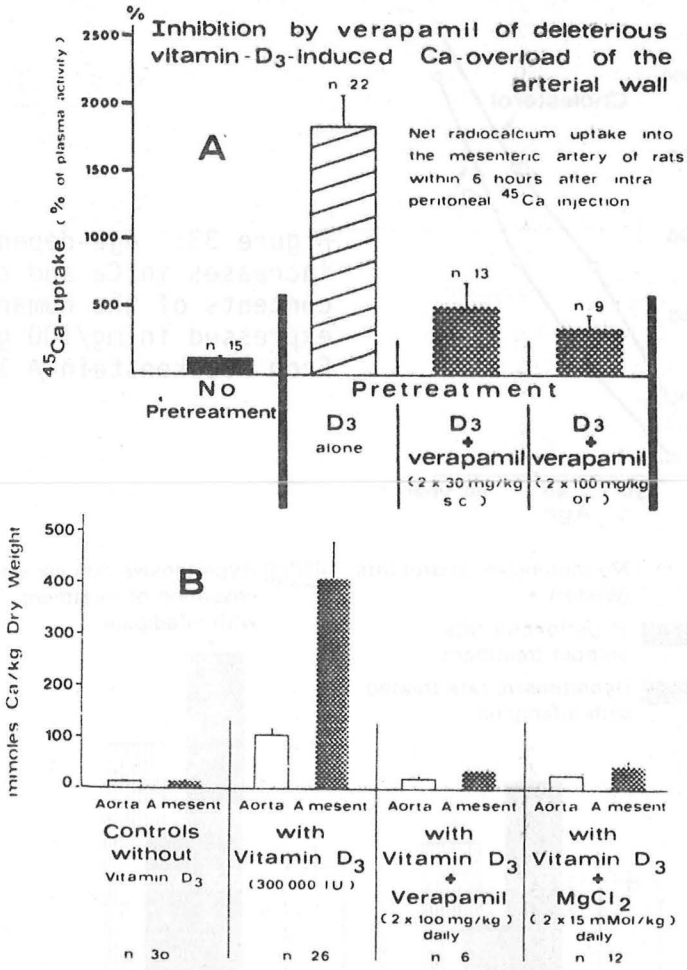


Figure 35: Inhibition of vitamin-D,-stimulated (300,000 IU/kg) net radio-calcium uptake into the wall of the mesenteric artery of rats by verapamil, administered subcutanously or orally for four days. Prevention of vitamin-D,-induced (300,00 IU/kg) rise in absolute Ca content of the aortic and mesenteric walls by oral treatment with verapamil or $MgCl_2$,for four days. From Fleckenstein A et al 1983A.

In the spontaneously hypertensive rats, calcium content of the arterial wall increases in contrast to the normotensive animals. Chronic treatment of the hypertensive rats attenuated the abnormal augmentation of Ca in the vessels, and discontinuation of therapy results in tendency to reaccumulate

calcium (Fleckenstein 1983A). These observations provide further evidence of vascular protection by Ca antagonists. It is unclear, however, whether the beneficial effect was due to the drug action or due to blood pressure reduction. Much work remains to be done to test this phenomenon in human atherosclerosis.

Potential Therapeutic Benefits of Calcium Antagonists in A Variety of Other Conditions

The potential usefulness of calcium antagonists has been noted in a variety of conditions other than hypertension, coronary artery disease, and cardiac arrhythmias.

- Intracerebral hemorrhage (Allen et al 1983) and cerebral arterial spasm (Allen 1985)
- Raynaud's phenomenon (Smith and Roderheffer 1985, Nilsson et al 1984)
- Migraine (Gelmers 1985, Gelmers 1983)
- Hypertrophic cardiomyopahty (Rosing et al 1985, Sonnenblick et al 1985)
- Pulmonary hypertension (Rubin et al 1983, Packer 1985)
- Asthma (Patakas et al 1983, Fanta 1985)
- Esophageal Spasm (Bortolctti and Labo 1981, Castell 1985)
- Inhibition of platelet functions (Ikeda et al 1981, Mehta 1985)

In the above disorders, clinical experience with calcium channel antagonists is limited and inconclusive. Additional trials will shed more light on the therapeutic efficacy and usefulness of calcium channel antagonists in an assortment of cardiovascular and non-cardiovascular disorders. It is apparent, however, that calcium fluxes may mediate as a pathogenetic factor in a number of hithertofore poorly understood diseases.

It is possible that owing to their structural heterogeneity, some calcium antagonists may be effective only in certain conditions, not in others i.e. there may be tissue selectivity. For example, nimodipine selectively dilates cerebral vessels. With more research and further delineation of structural-activity relationships, a specific calcium antagonist can be selectively used for a specific disorder.

New Generation Calcium Antagonists - A Concept Based on Tissue Selectivity

Initially, calcium antagonists were introduced for their actions on the heart - to decrease automaticity, AV conduction, cause coronary artery relaxation, etc.. Soon it became evident that various compounds which we have come to recognize as calcium antagonists exert actions not only on different aspects of cardiac cycle but they also had the propensity to cause peripheral vasodilation. It became clear that the so-called calcium antagonists manifested a bewildering heterogeneity in chemical structure and were not selective for myocardium or vascular smooth muscle. This led Fleckenstein to classify calcium antagonists into 2 categories - Group A comprising of potent calcium antagonists e.g. nifedipine, verapamil, diltiazem and Group B comprising of less active drugs e.g. fendiline. This simple classification may no longer be adequate to explain the spectrum of physiological and pharmacological effects of calcium antagonists. Whereas

a truly cardioselective agent that spares the peripheral vasculature has not been found, the converse is true. For example, cinnarizine and flunarizine in vivo appear to exert their action solely on the vascular smooth muscle (Van Neuten adn Vanhoutte 1981). Radioligand binding studies have demonstrated that calcium antagonists display a diverse range of actions toward selective tissues, a prospect that is bound to have far reaching therapeutic possibilities (Singh et al 1985).

Brief Comments on Selected New Generation Calcium Antagonists

GALLOPAMIL (D-600) AND TIAPAMIL: These compounds resemble verapamil. Their major electrophysiological actions are on the AV conduction and automaticity. Although unpublished observations suggest that gallopamil may be highly selective and effective in terminating supraventricular tachycardias, comparative clinical studies are not available. Recently tiapamil was shown to lower the systolic hypertension in the elderly without any adverse effects (Balansard et al 1984).

NIMODIPINE increases cerebral blood flow with beneficial effects in cerebral ischemia. It may also be useful in migraine.

NITRENDIPINE is a dihydropyridine derivative like nifedipine and nimodipine. Its peripheral vascular effects are more prominent than the cardiac effects making it an effective antihypertensive agent (Ram et al 1984B). What advantage it would have over nifedipine is not determined.

NISOLDIPINE is a potent afterload reducing agent with a long elimination life (> 10 hours) which may be advantageous in the treatment of hypertension in terms of patient compliance. Like nifedipine, it does not have a negative effect on AV conduction or myocardial contractility (Singh et al 1985).

NICARDIPINE may be useful in the treatment of hypertension as well as angina. However, in the formulation that is available in the United States for experimental use in hypertension, it has to be given in a t.i.d schedule (Ram CVS et al unpublished observations). A preliminary report indicates that this drug may have a favorable effect on cerebral vasculature (Gheorghiade et al 1985) which should prove to be advantageous in the treatment of hypertension.

PIPARAZINE DERIVIATIES (FLUNARIZINE AND CINNARIZINE) appear to have predominantly vascular relaxant effects. Their clinical utility in hypertension is yet to be investigated but promising results have been obtained in patients with primarily circulatory disturbances such as migraine, veretebrobasilar insufficiency, and peripheral vascular disease (Holmes et al 1984). Lidoflazine dilates coronary and systemic arteries. Information on its electrophysiological effects is scant.

BEPRIDIL has an unusually long elimination half-life (40 hours). It appears to be effective both in ventricular and supraventricular tachyarrhythmias, a property not shared by other calcium antagonists. It appears to exert moderate anti-hypertensive effects (Ram et al unpublished observations).

In summary, we have taken a glimpse at some of the second generation calcium antagnoists. Much work remains to be done to document their efficacy, safety, and adverse effects in the long term treatment. Some of these agents appear to be more refined in their actions on various organ systems and likely their use can be targeted to specific pathophysiological entities. Further therapeutic advances in the development of tissue selective calcium antagonists are already in the offing and the future holds considerable promise for the availability of drugs with well defined therapeutic spectrum.

Unanswered Questions

So far the clinical experience with calcium channel antagonists has been generally gratifying. However, their use should not be without discretion and without a clear indication. Calcium ions are important in regulating various physiological and homeostatic processes, and unwanted inhibition of calcium fluxes may be potentially harmful although fortunately thus far this has not been witnessed. Several aspects of calcium antagonists will need clarification by clinical experience:

1) What are the long term benefits of calcium antagonists in hypertension? In the dosages clinically employed, will these agents offer an advantage over the currently used anti-hypertensive agents in preventing atheroslcerotic complications (like myocardial infarction)?

2) What are the consequences of calcium antagonism on the calcium metabolism itself?

3) Can the vital secretory processes be affected by calcium antagonism?

4) Since some calcium antagonists may suppress aldosterone secretion (at least in the short term), can these compounds prevent or minimize hypokalemia resulting from diuretics and other causes of secondary aldosteronism? In other words, can these compounds suppress abnormal aldosterone secretion?

5) Is it possible to develop compounds that stimulate rather than block the calcium channel? Such compounds may offer a therapeutic hope in disorders where calcium dependent functions may be pathologically depressed (Towart and Schramm 1984).

Conclusions

It is rare in the history of medicine for more than one scientific discipline to be so greatly influenced as is the case with calcium antagonists. Since calcium ions subserve a vital role in many physiological functions and even pathophysiological derangements, agents that interfere with cellular actions of calcium have considerable therapeutic potential. Besides various cardiovascular disorders, calcium antagonists may have a beneficial effect in the management of hypertension. By their unique action, these agents may actually attack the pathophysiological mechanism(s) in hypertension, thus creating a rational approach to treatment. If the presently promulgated concepts are true,

calcium antagonists lower the blood pressure while maintaining or even restoring the tissue circulation. And this may result in improved outcome from chronic drug therapy.

While none of the calcium antagonists have been approved by the FDA for routine clinical use in hypertension, it is already apparent that they are quite useful and indicated in several clinical settings. Nifedipine is effective in the management of acute, severe, or refractory hypertension. It may be used as a third line agent when the blood pressure is not controlled with more conventional agents. Both verapamil and diltiazem lower the blood pressure in mild to moderate hypertension and they may be more suitable for monotherapy as an alternative to diuretics or beta-blockers but additional experience is warranted in this area.

The calcium antagonists constitute a structurally diverse group of agents that exhibit varying degrees of potency. The net actions of these agents represent a balance of direct and indirect autonomically mediated actions. A knowledge of the pharmacodynamic differences between these drugs dictates the choice of the appropriate agent for any given situation. Since the full spectrum of the intended and adverse effects of these drugs is not established, caution is advised in using them for uncertain indications. Comprehension of the newly acquired information should provide the stimulus for further research and for the reconsideration and reappraisal of our currently accepted hypotheses and therapeutic principles.

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