

# NEW TRENDS IN ANTI-HYPERTENSIVE THERAPY, CALCIUM CHANNEL ENTRY BLOCKERS

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Hypertension remains one of the most common prevalent disease world wide. The physicians' attitude towards raised blood pressure levels has changed progressively over the past two decades with growing awareness of the risks associated with even relatively minor increase in arterial pressures and the development of more acceptable and safe antihypertensive drugs.

Antihypertensive treatment like all other fields of cardiovascular medicine has undergone significant advancement in the past few years.

Since the introduction of drug therapy for hypertension several drugs have become obsolete. Alpha methyl dope was the major drug until recently. Then came the Beta adrenoceptor blockers, vasodilators and more recently, angio. tensin converting enzyme inhibitors and calcium channel entry blockers. Thiazide diuretics have, however, remained a viable group throughout. The physician has a wide range of agents to choose for a particular patient situation. Useful combination therapies have emerged to deal with refractory, severe, accelerated/malignant hypertension and the hypertensive emergencies. There is good evidence to suggest that effective blood pressure control has resulted in the decline of its complications.

The advent of calcium channel blockers for the control of hypertension has gained a lot of interest in the last few years. Today three pharmacological agents representing three classes of calcium channel blockers are commercially available i.e., Nifedipine, Verapamil and Diltiazem which are in use in USA and UK and available in Pakistan as well.

Belonging to same therapeutic group, the three have differences in their mechanism of action and clinical application. With the passage of time our understanding of their mechanism of action has improved and a number of new indications for their use have emerged. In this article it is proposed to discuss the use of Calcium Blockers in hypertension.

## MECHANISM OF ACTION

Ca<sup>+</sup> transport in the cardiovascular smooth muscles has three possible sites. The main pathway is perhaps the so called voltage dependent channel, controlled by a "gate" that opens and closes in response to voltage gradient. Ca blockers close this gate and thus inhibit the entry of extra cellular Ca<sup>+</sup> into this channel. This blockage results in the reduction of available Ca for contractile processes.

Besides inhibiting the intracellular entry of Ca ions they also inhibit the rate of Ca binding<sup>1</sup>.

The second pathway is the Receptor Dependent Channel, normally activated by alpha agonist Norepinephrine and angiotensin and related endogenous substances. On interaction of agonist with the receptor this channel is opened and the extracellular Ca enters into the cells. This channel activation also mobilizes Ca from the inactive intracellular stores.

By their competitive blockade of the effects of Norepinephrine by an action on alpha adrenergic receptors some Ca blockers may block the receptor dependent channel<sup>2</sup>.

The third pathway is dependent on Na — Ca exchange across the cell membrane. This pathway is (somewhat) indirectly affected. The Ca blockers block the entry of ionic Calcium into the cells. This impedes the role of Ca as intracellular ionic messenger which initiates Na - Ca exchange. These drugs do not antagonize the effects of Ca; they merely prevent the ions from entering the intracellular site of action. Hence Ca channel blockers is the preferred term over Ca antagonist<sup>3</sup>. As mentioned earlier despite common biological and pharmacological properties there exist notable differences in the mechanism of action of three sub groups of Ca blockers. The three groups include Diphenyl

alkylamines, Benzothiazepines and Dihydropyridines represented commercially by Verapamil, Diltiazem and Nifedipine respectively.

It has been postulated that three specific receptor sites exist one each for Nifedipine, Verapamil and Diltiazem.

## **ANTI HYPERTENSIVE ROLE**

One of the greatest incentives for the advent of calcium blockers came from the concept that Ca as opposed to other agents such as Na may be the primary agent in the genesis of essential hypertension.<sup>4-5</sup> However the statistical relationship between Ca and the BP is weak except only in studies involving large patient population<sup>6</sup>.

The interest in this class of agents was aroused because they were considered desirable antihypertensive agent and perhaps a class of drugs which may well serve as a single therapeutic agent for certain types of hypertensive patients.<sup>7</sup> In contrast to many other antihypertensive agents like diuretics and beta blockers pharmacologically effective drug concentration of Ca blockers capable of effective BP control have been shown to have no effect on the secretion of glucoregulatory hormones in human.<sup>8</sup> Therefore, they are safer and more logical for those hypertensive patients who also suffer from diabetes. Similarly in contrast to B blockers, Ca blockers may cause slight increase in the cardioprotective heavy density lipoprotein (HDL) and do not adversely affect the serum cholesterol and triglyceride levels. Since most of the patients with metabolic disorders also suffer from coronary artery disease in addition to hypertension, Ca blockers may be considered as effective therapy for the simultaneous alleviation of both of these symptoms without aggravating the metabolic disorder. Another major subgroup of patients to benefit from Ca blockers is elderly (over 60 years) hypertensive. It has been noted that the decrease in BP after the administration of Ca blockers tends to correlate positively with patient's age and relates inversely to the patient's pre-treatment plasma renin activity<sup>9</sup>.

The relative ineffectiveness of B blockers as well as the high efficacy of Ca blockers in the elderly patients may be due to plasma renin activity gradually declining with age. Similar effect is also noted in black hypertensives of all ages who fail to respond to B blockers despite marked reduction in heart rate. Again low plasma renin activity as compared to whites is the possible explanation. Unlike many vasodilators significant tachycardia and a very hyperdynamic circulation is not generally induced by Ca Blockers.

Ca blockers like Nifedipine are very useful in the hypertensive emergencies. Sublingual Nifedipine is an effective therapy bringing results in 1-5 minutes.<sup>11</sup> Patients with impaired renal function and hypertensive crisis also tend to benefit from Nifedipine. When hypertensive encephalopathy occurs in such patients Nifedipine can reduce or completely alleviate its symptoms.<sup>12</sup> Acute episodes of hypertension with pregnancy and pregnancy associated hypertension can be effectively dealt with Nifedipine without adverse effects on foetus.<sup>13</sup> Classically speaking Ca blockers are grouped as second or third line agents in the order of antihypertensive regimens. However, such strict protocols are no longer followed. Many studies have supported their use as effective first line single agents. In some situations, they become the drugs of first choice on their own merits as shown above.

### **NIFEDIPINE (ADALAT R PROCARIDAR)**

This is the oldest and perhaps the most widely studied agent. Several studies support its use as a single agent in the treatment of uncomplicated hypertension. Double blind cross-over studies have compared Nifedipine with Diltiazem and Verapamil. Results have shown comparable efficacy of all three agents.<sup>14</sup> Side effects were more common with Nifedipine when compared with Verapamil. However more sustained control was noted. As far as negative inotropic effect on the myocardium is concerned it

is the least probable with Nifedipine, less with Diltiazem and most probable with Verapamil. Nifedipine has been successfully used both in acute and chronic heart failures when an antihypertensive drug is required on a short or long term basis.<sup>15</sup> In fact S/L Nifedipine has been used as an initial and only agent in the treatment of Ac Pul oedema in patients with decompensated hearts due to severe hypertension.<sup>16</sup> Most of these effects are due to potent after load reduction. In addition to mono therapy various useful combinations have emerged using Nifedipine as a second or third drug. Studies involved concomitant use of Thiazide diuretics, B blockers, methyl dopa, captopril in moderately severe to severe hypertension with good results. Combination of Nifedipine and Benzothiazide has been shown to be safe and effective achieving more of a reduction in BP in the supine and standing positions than with either drug alone. This is a relatively inexpensive regime. In some patients Nifedipine may actually be a third step drug of choice.

Lack of postural effects with Nifedipine are striking.<sup>17</sup> However, it is a very potent hypotensive agent and when combined with certain other anti-hypertensive drugs like Prazocin it may cause sudden precipitous fall in BP levels. This may have serious consequences. Sublingual Nifedipine used in hypertensive emergencies, though very effective and prompt, at times drops the levels dramatically and can be problematic. Therefore it merits a very close monitoring.

#### **Dosage:**

Adalat 10 - 20 mg. TID. Adalat Retard 20 mg. BID. Common side effects are headache, fluid retention and constipation.

#### **VERAPAMIL (CALAN R ISOPTIN R)**

This drug, previously used only for the treatment of arrhythmias and angina pectoris, has recently been approved as antihypertensive agent in USA. In addition to sharing the effects of Ca<sup>++</sup> channel blockers on the smooth muscle cells of blood vessels and myocardium as discussed above, Verapamil is especially effective in Ca channels that have a high frequency of opening and closing, a pattern that occurs in sinus and AV node, hence its usefulness in the control of supra — ventricular arrhythmias. As a matter of fact Verapamil is the drug of choice for the treatment and control of paroxysmal supra ventricular tachycardia in many centres. Comparative studies with Nifedipine and Diltiazem have shown that Verapamil is equally effective in lowering BP. Out of the three agents Verapamil is known to have most negative inotropic effect in long term treatment. In Ac severe congestive cardiac failure intravenous administration of Verapamil in moderate doses does not decrease LV function.<sup>18</sup>

Comparative studies with Propranolol and Atenolol have shown equal effectiveness.<sup>19</sup> In another study it was found more effective than Propranolol in black hypertensives. Verapamil can be given with Thiazide diuretic for additive effect but very few studies are available on concurrent use with beta blockers and ACE inhibitors.

#### **ADVERSE EFFECTS**

Serious adverse reaction to Verapamil are uncommon. But heart failure, hypotension, bradycardia and various A.V. blocks can occur, particularly in patients with severe L.V. Dysfunction and S.A. Node or A.V. Node conduction disturbances.

Less serious side effects include constipation, oedema, headache and fatigue. Hepatic toxicity and impotence has been reported. The safety in pregnancy is not determined. The drug is excreted in human milk and, therefore, should not be given to nursing mothers.

Verapamil increases the toxicity of digoxin and quinidine and related drugs.

Dosage: The antihypertensive dose; 80 mg.

TID or one tablet of 240 mg. S.R. (sustained release tab) to be taken in the morning. Maximum daily dose is 360 mg. beyond which its further effectiveness is doubtful.

Diltiazem (Herbesser R Cardiazem, R Tailiazem R) This is the newest of the three agents.

Most of the initial clinical trial reports are from open studies conducted in Japan<sup>20</sup>. Most of these studies were done on patients with mild to moderately severe hypertension and the drug was used as an

additive agent. These early trials suggested good antihypertensive effect with fewer side effects. However, these studies involved small patients groups.

Maeda et al studied 28 patients with all severities of hypertension. In this study Diltiazem was used alone and in combination with thiazide diuretic. Fifteen normotensives served as control group. Used as monotherapy systolic pressures were reduced by 89 to 67% respectively. Mean systolic and diastolic pressures were not affected in Normotensive control group. In combination with thiazide group all patients responded including those who failed to Diltiazem mono-therapy. All patients received 180 mg of drug daily. Significant hypotensive effect was shown after one week and it was stabilised at lower levels after 6-8 weeks of therapy.

Comparative short term trials with Nifedipine have shown similar reduction in systolic and diastolic levels at rest and exercise. However, Diltiazem had no effect on Pulmonary Vascular resistance, whereas Nifedipine caused a substantial decrease. Heart rate was decreased in Diltiazem group but increased in Nifedipine.

Comparative studies with B blockers have shown approximately the advantages and results as hold true for the Ca-Blockers as a whole.

In a comparative study with Propranolol Yamakado (1983) treated 16 patients with Diltiazem 180 mg or Propranolol 60 mg daily. Propranolol was more effective at exercise particularly in lowering systolic blood pressure. At rest Diltiazem decreased mean systolic and diastolic pressures. At rest Propranolol decreased heart rate more than Diltiazem at rest and exercise. Thus the antihypertensive effect of Diltiazem was less potent than Propranolol, but at rest and during exercise there were lesser negative inotropic and chronotropic effects.

In a recent multicentre randomized placebo controlled trials Diltiazem was studied as a monotherapy for systemic hypertension. This study involved 77 patients (40 Diltiazem and 37 Placebo) with stable supine diastolic pressures between 95 and 100 mm Hg. Previous antihypertensive therapy was withdrawn 4 weeks prior to trial. The drug was titrated to optimal dose and followed for a total of 12 weeks during therapy. A Diltiazem dose of 360 mg/day was required in 85% of patients. Average BP in all positions was significantly reduced by Diltiazem compared to Placebo. There was no significant change in heart rate at week 12. Diltiazem showed better responses in older patients but caused no increase in orthostatic BP drops. Only 1 patient receiving Diltiazem stopped therapy as a result of adverse effects, compared to 2 in the placebo group.

This study has shown clear advantages of Diltiazem. The lack of reflex tachycardia represents an important advantage over vasodilators and Ca-Blocker Nifedipine. Orthostatic effects were virtually absent. Though Ca-Blockers as a whole have better results in older patients this study showed a somewhat greater effect of Diltiazem in older subjects. Adverse effects were insignificant, i.e., mainly dizziness, headaches and oedema. This study concluded Diltiazem as an effective monotherapy for mild to moderate essential hypertension, comparable to most other first line agents. Given its benign side effect profile clear advantages in certain subsets of patients particularly elderly and those with stable to unstable angina makes Diltiazem a promising first line antihypertensive agent.

**Dosage:** The recommended antihypertensive dose is 30-60 mg. TID.

## CONCLUSION

1. Ca-Channel Blockers have proven to be effective antihypertensive agents.
2. They have no metabolic adverse effects and are therefore preferred drugs in Diabetic and Hyperlipidaemic subjects.
3. With the slow release preparation of Nifedipine and Verapamil they have the convenience of dosage.
4. In certain group of Hypertensives they may be the first choice drugs. These include:
  - a) Patient with Coronary Artery Disease.

- b) Presence of Concomitant Pulmonary Hypertension.
  - c) Elderly
  - d) Black Hypertensives.
  - e) Patients with Compromised Hearts.
  - f) Patients with supra ventricular arrhythmias.
5. They have weak negative inotropic effect as compared to Beta Blockers.
  6. They are equally effective at rest and at exercise.
  7. In contrast to other vasodilators they do not produce significant reflex tachycardia or hyperdynamic circulatory states.
  8. They have a relatively benign side effect profile as compared to most antihypertensive agents.
  9. They are shown to have a regressive effect on left vent hypertrophy.
  10. Diltiazem is generally recognized to produce fewer adverse effects among three agents available is potentially the most attractive agent to evaluate.

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