Sustained Release Verapamil In Hypertensive Patients

*SHAHID KARIM**
*NADEEM HAYAT MALIK***
*AFTAB TARIQ****
*M. ZUBAIR*****

Summary:

Thirty patients (22 females and 8 males) were put on Verapamil SR, a slow release calcium channel blocker, for three weeks on out door basis. Mean age was 44.3±2.5 years, mean weight before treatment was 67.1±24 Kg, after treatment it was 64.7±3.5 Kg, mean height was 156±3 Cm and mean duration of hypertension was 3.89±1.5 Years. Mean supine systolic pressure decreased from 164±2.33 mmHg to 140±6.5 mmHg (P<0.01) while supine standing pressure decreased from 163.6±4.1 mmHg to 147.5±04 mmHg (p<0.01). Fall in mean supine diastolic pressure was from 107.33±1.14 mmHg to 91±4.2 mmHg (P<0.01) while fall in standing diastolic pressure was from 110±1.7 mmHg to 97.3±2.1 mmHg (p<0.001). Mean supine arterial pressure decreased from 126 mmHg to 107.3 mmHg while standing mean arterial pressure decreased from 127.9 mmHg to 114 mmHg. No statistically significant fall in heart rate both in supine and standing position was observed. Laboratory results did not show any variation. In 72% of the patients supine systolic pressure was ≤ 150 mmHg while in 32% of the patients supine diastolic pressure was ≤ 90 mmHg. Verapamil SR was found moderately effective and safe in controlling mild to moderate hypertension.

Introduction:

Calcium channel blockers are used now in various important therapeutic implications. These drugs are found effective in the management of ischaemic heart disease, peripheral vascular disease, hypertension, supraventricular arrhythmias and other non cardiovascular conditions. Calcium antagonists are now in use for the treatment of hypertension widely. These drugs cause fall in blood pressure in hypertensive patients not only at rest but also during physical activity. Now calcium antagonists can be considered as monotherapy[1] in patients with essential hypertension. Calcium antagonists have no detectable effects on insulin secretion in human pancreas[11]. Verapamil is a papavarine derivative[3]. Verapamil was first proposed for the treatment of hypertension during 1968. However, it has not been until recently that serious attention has been given to its use in the management of hypertension. 70% of the drug is eliminated via kidneys and 15% drug is eliminated via GIT route. Cocomitent administration of Cimetidene may increase serum Verapamil level[3]. Increased peripheral vascular resistance is the hallmark of systemic hypertension[3,5,10]. Verapamil decreases blood pressure by decreasing peripheral vascular resistance[2,10] with little decrease in cardiac output or heart rate, as a result of negative chronotropic and ionotropic effect and so decreases both systolic and

* Registrar, Cardiology Deptt., Mayo Hospital, Lahore.
** Assistant Professor, Cardiology Deptt., Mayo Hospital, Lahore.
*** Registrar, Cardiology Deptt., Mayo Hospital, Lahore.
**** Head of the Cardiology Deptt., Mayo Hospital, Lahore.

diastolic pressure[3-9]. Verapamil is found relatively safe and well tolerated by the young patients and as well as by the elderly patients[3]. Verapamil can be used as step I monotherapy for essential hypertension[3]. Sustained release Verapamil can be used as single daily dose in hypertensive patients[14,15].

Patients and Method:

Thirty patients (22 females and 8 males) with mild to moderate essential hypertension were put on sustained release Verapamil 240 mg once a day for three weeks. All the patients were taking antihypertensive drugs to which they were either not responding or were not tolerating the side effects of the drug. Antihypertensive drugs were stopped at least one week before starting treatment with sustained release Verapamil. Blood pressure was measured with the same mercury sphygnomanometer, by the same observer, both in supine (10 minutes after rest) and standing (2 minutes after standing) position at the same time of the day. Phase I and phase V of Kortokoff sounds were taken as systolic and disastolic pressure. A complete history was taken before the treatment and physical examination of the patients was carried out during the first and last week of treatment. X-Ray chest and ECG were taken before starting the treatment and at the end of treatment period. Patients were advised to come weekly, empty stomach between 8.00 A.M. to 11.00 A.M.

General Information

TABLE NO. 1

	No.	
Total No. of patients	30	
Male patients	8	
Female patients	22	
No. of patients who completed the study	24	
No. of patients lost during follow up	3	
No. of patients withdrawn from the study	3	
Duration of study	3	weeks
Dose of the drug	240	mg O.D.

Inclusion Criteria:

Male or female patients, aged 18-75 years.

Essential hypertensives either newly diagnosed/ established hypertensives not controlled with other drugs.

Mean supine diastolic pressure 95-115 mmHg.

Mean supine systolic pressure 140-200 mmHg.

Informed consent of the patient.

Exclusion Criteria:

Accelerated or secondary hypertension.

Active liver disease or chronic liver impairment.

Congestive cardiac failure, severe ischaemic heart disease.

Complete atrioventricular block.

Sick sinus syndrome.

Asthma or chronic obstructive air way disease.

Peripheral vascular disease.

Renal insufficiency with plasma creatinine ≥ 130 micro mol/L Diabetes Mellitus.

Plasma Potassium ≤ 3.0 mmol/L or ≥ 5.5 mmol/ L or plasma sodium ≤ 130 mmol/L.

Treatment with drugs known to affect the blood pressure.

Any chronic disease requiring long treatment.

Pregnancy or lactation.

Hypersensitivity to any of the test material or related compounds.

Unwillingness or inability to conform to the protocol.

After completing the trial, the results of the patients who completed the trial were subjected to statistical analysis. A paired t test was used for assessing the significance of the differences between mean values of all the values. All tests used were two tailed and $p \leq 0.05$ was considered as the upper limit of the significance. Results are expressed as means and standard error of means.

Patient Characteristics

TABLE NO. 2

Mean Age	44.3±2.5 years
Mean duration of hypertension	3.89±1.5 years
Mean weight of the patients	67.1±2.4 Kg
Mean height of the patients	156±3 cm

Sitting Blood Pressure and Pulse Rate

TABLE NO. 3

	Before Treatment	After Treatment
Systolic Pressure	164±2.33 mmHg	140±6.5* mmHg
Diastolic Pressure	107±0.33 mmHg	91±4.2* mmHg
Heart Rate	89.2±2.4 /min	81.9±4 /min
Arterial Pressure	126 mmHg	107.3 mmHg

*p value ≤ .01

Statistical Analysis:

Thirty patients, 22 females and 8 males were enrolled for this trial. Mean age was 44.3±2.5 years, (range 28-60 years), mean weight before treatment was 67.1±2.4 Kg (range 47-95 Kg), after treatment it was 64.7±3.5 Kg, mean height was 156±3 Cm (range 145-170 Cm) and mean duration of hypertension was 3.89±1.5 Years (range 0.5-10 years).

Twentyfour (80%) patients completed the trial. 3 patients were lost during follow up. 3 patients were withdrawn from the study due to side effects. 15 patients were on tab. Aldomet, 5 patients were on Indipamide, 2 were on Atenolol, 2 were on Captopril, 2 were on Propranolol, 2 were on Nifedipine and one patient was on tab. Pindolol. None of these patients was smoker. All patients were married.

Results:

Mean Supine systolic pressure before treatment was 164±2.33 mmHg and after treatment of three weeks with Verapamil SR it decreased to 140±6.5 mmHg while supine diastolic pressure before treatment was 107.33±1.14 mmHg and after three weeks it was decreased to 91±4.2 mmHg. Mean standing systolic pressure dropped from 163.6±4.1 mmHg to 147.5±4.04 mmHg and mean diastolic pressure decreased from 110±1.7 mmHg to 97.3±2.1 mmHg. In 40% patients supine systolic pressure was ≤ 140 mmHg while in 72% patients it was ≤ 150 mmHg after three weeks treatment. In 32% patients supine diastolic pressure was ≤ 90 mmHg and was ≤ 95 mmHg in 48% of the patients.

Mean arterial pressure (1/3rd systolic + 2/3rd diastolic) in supine position dropped from 126 mmHg to 107.3 mmHg while standing mean arterial pressure decreased from 127.9 mmHg to 114 mmHg. (See Table No. 1).

Mean pulse rate in supine position dropped from 89.2±2.4/min to 81.9±4/min while drop in mean standing pulse rate was from 89.2±2.4/min to 89.5±4.4/min. No statistically significant fall in heart rate was observed in this study as observed by others[1,4,5,9] in supine position.

Laboratory Results:

No statistically significant differences were observed in laboratory tests during three weeks therapy with Verapamil SR.

In our study serum cholesterol, triglycerides, HDL, LDL, Uric acid and serum electrolytes etc. were not altered significantly during three weeks time period. X-Ray chest did not show any change after treatment. Blood complete examination did not reveal any significant abnormality after completion of trial. ECG before treatment and after treatment was the same in all the patients.

Standing Blood Pressure and Pulse Rate

TABLE NO. 4

	Before Treatment	After Treatment
Systolic Pressure	163.6±4.1 mmHg	147.5±4.04* mmHg
Diastolic Pressure	110±1.7 mmHg	97.3±2** mmHg
Heart Rate.	89.2±2.4 /min	89.5±4.4 /min
Arterial Pressure	127.9 mmHg	114 mmHg

*p value ≤ .01

** p value ≤ .001

Side Effects:

Side effects were evaluated with both, the spontaneous complaints by the patient and by direct questioning with the patient every week. 3 patients were withdrawn from the study due to intolerance to treatment. Some studies have reported an adverse reaction rate of 20% to 57% with Verapamil[11] but no serious side effects were observed by these authors. It was found well tolerated by most of the patients[2,3,15] feeling of sickness, nausea, vomiting, constipation,[6] (in 12% to 42% cases has been reported)[11] which is due to smooth muscle relaxing property of the drug[11]. Diarrhoea, flushing, headache, pruritis[2,4] etc. has been reported also. After intravenous administration of Verapamil asystole and hypotension has been observed[12] 1st[2], IInd and Third degree heart blocks have been documented in different studies[3]. Hypotension, ankle edema, palpitation, chest pain, heart failure are also reported[11,13]. All the complaints were mild and were well tolerable. Headache and flushing are due to vasodilatation effect of the drug[11].

In our study patients complained of lethargy, leg cramps, oedema feet, headache, palpitation, constipation, nausea and flushing of the face. 9 patients had no complaint at all. Patients who were withdrawn from the study have severe headache, flushing of the face, palpitation and lethargy which were intolerable to these patients.

Adverse Events

TABLE NO. 5

Name	No. of Side Effects
Lethargy	2
Palpitation	2
Nausea/vomiting	2
Oedema feet	1
Constipation	3
Headache	3
Facial flushing	3
Leg cramps	2

Note:-Nine patients had no complaint at all while rest of the patients had one or more complaints.

Discussion:

This study done to evaluate the effect of Verapamil SR, shows that patients with mild to moderate hypertension has a decrease in their blood pressure both in Supine and standing position but slowly during three weeks time. Verapamil SR for a short period of time has been found effective in hypertensive patients by others also. Antihypertensive action of Verapamil is found greater in low renin level elderly than in high renin level young hypertensives[2]. However, plasma renin activity was not measured in our study. The dose given to get antihypertensive effect is almost similar to which is given for antianginal therapy but now this was in sustained release form using single dose. Verapamil SR has not much influence over heart rate both in standing and supine position. None of the patients receiving Verapamil SR had a heart rate lower than 50/minute. Our study on 30 patients shows that Verapamil SR is effective for short term therapy in patients with mild to moderate hypertension. Long term therapeutic efficacy of Verapamil SR has been demonstrated by other investigators[14]. Increase in end diastolic left ventricular pressure after Verapamil therapy has been found[11].

A theraputic failure to treatment is commonly defined as an insufficient response to a specific drug treatment. Sometimes drug treatment produces effects opposite to those intended. Systolic BP was

increased during Verapamil therapy in 1 patient so therapeutic failure was 5%.

Verapamil SR was well tolerated by most of the patients. Only three patients were withdrawn from the study due to serious side effects. Considerable attention has been given to observe metabolic adverse effects of the drug. Verapamil SR had no effect on S. triglycerides, S. cholesterol, S. HDL, S. LDL and S. Uric acid level during three weeks time.

Conclusion:

Treatment with Verapamil SR as monotherapy for patients with uncomplicated mild to moderate essential hypertension demonstrate that it is an effective, well tolerated and safe means to achieve goal to control blood pressure in patients with mild to moderate hypertension. It has a few side effects. No adverse effects were observed on biochemical parameters. More controlled long term studies are still required to establish whether Verapamil SR retains its antihypertensive efficacy and safety during long term treatment.

Acknowledgement:

We acknowledge the contribution of Mr. Muhammad Mazhar Khan, Senior biochemist, Mayo Hospital, Lahore, who has performed all the laboratory tests.

References:

1. Jaap Mooy, Marleen Van Baak, Roland Bohm, Ronald Does, Hans Petri, Judith Van Kemenade, Karl H. Rahn. The effect of Verapamil and propranolol on exercise tolerance in hypertensive patients. Clin Pharmacol Ther 1987; 41:490-495.

2. Luigi X Cubeddu, Juan Aranda, Bramah Singh, Michael Klein, Jonas Brachfeld, Edward Freis, Jorge Roman, Thomas Eades. A comparison of Verapamil and propranolol for the initial treatment of hypertension. (JAMA 1986; 256:2214-2221).

3. Jack A Stroh, William H. Frishman. Verapamil in the treatment of hypertension. CVR & R Aug. 1987; 8:1-5).

4. Jorge Escudero, Hector Hernandez and Froylan Martinez. Comparative study of the antihypertensive effect of Verapamil and Atenolol. (Am J Cardiol 1986; 57:54D-58D).

5. Roland E., Franz H., Guillermo E. and Boris D. Cardiovascular effects of Verapamil in patients with essential hypertension. (Circulation 1987; 75 No. 5 1030-1036).

6. Paolo Stadler, Luca Leonardi, Walter Riesen, Walter Ziegler, Claudio Marone and Carlo Beretta. Cardiovascular effects of Verapamil in essential hypertension. (Clin Pharmacol, Ther 1987; 42: 485-492).

7. Franz H. Messerli. The age factor in hypertension. (Hospital Practice Jan. 15 1986).

8. F.R. Buhler, U.L. Huithen, W. Kiowski and P. Balli. Beta blockers and calcium antagonists, corner stones of antihypertensive therapy in the 1980s. (Drugs 1983; 25; suppl-2 50-57).

9. Franco B. Muller, Peter Bolli, Paul Erne, Wolfgang Kiowski, Fritz R. Buhler. Calcium antagonism—A new concept for treating essential hypertension. (Am J Cardiol 1986; 57: 50D-53D).

10. W. Klein et al. Role of calcium antagonists in the treatment of essential hypertension. (Cir Res. 1983; 52: supple. II: 174-181).

11. Rolef Krebs M.D. Adverse reaction with calcium antagonists. (Hypertension; Sup. II. 1983 Vol. 5 No. 4: 125-128).

12. Werner W. Kelin. Treatment of hypertension with calcium channel blockers. European Data. A Jor Med. 1984; 77(4A) 143-146).

13. J.A. Henry, P.C. Chester, A.N. Latham. Sustained Release Verapamil or Atenolol in essential hypertension. Journal of Drugs July 1988 Vol. 1 No. 2. 69-75.

14. Reinfrank J, Eckardt A, Scheider G, et al. Long term efficacy and safety of Verapamil SR 240 mg in hypertension. Acta Therapeutica 1989; 15, 221-235.

15. Henry JA, Chester PC, Latham AN: Sustained Release, Verapamil or Atenolol in an essential hypertension. J Drug Dev. 1988; 1: 69-75.