24 HOUR STABLE ANTI-ANGINAL EFFECT OF RETARD VERAPAMIL, DILTIAZEM & NIFEDIPINE

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ABSTRAT

Background: Calcium autogonist are widely used as antianginal agents. Retard forms of calcium antagonists maintain anti anginal effect throughout 24 hours. However the duration of effect and antianginal effect of retard form of calcium antagonists has not been widely investigated.

Objective: The objective of this study was to asses the duration of effect, antianginal effect and tolerability of retard forms of nifedipine, verapamil and diltiazem.

Methods: Patients with typical exertional chest pain and atleast 1mm ST-segment depression on ECG were included in this study. Each patient under went control ETT. Then ETT was done after giving drugs at 4, 12 and 18 hours with each drug in all patients after an interval of 3-4 days. Mean ST-segment depression of all leads was calculated and Δ% ST-segment depression was derived. The drug was considered effective if Δ% ST-segment depression was more than 30%.

Result: With 20mg retard nifedipine, the Δ% ST-segment depression after 4 hours was 35.8% and after 12 hours was 45.2% with 120 mg retard verapamit, it was 36.4% after 4 hours 31.4% after 12 hours 25% after 18 hours with 240 mg of retard verapmit, it was 58.6% after 4 hours, 58.1% after 12 hours and 46.5% after 18 hours, with 90mg retard diltiazem it was 65.1% after 4 hours 49.9% after 12 hours and 16.4% after 18 hours.

Conclusion: All calcium antagonists in retard form have shown good anti ischemic and anti anginal effect throughout 24 hours.

INTRODUCTION

Calcium antagonist (CA) in retard forms retard exert stable anti-anginal effect throughout 24 hours. CA is widely used not only in cardiology but also used in other fields of medicine. In the beginning years, usual form of CA was not used widely. But in the last 10 to 12 years retard form of CA is in common use. By the use of retard form of CA, we can reduce daily consumption of total number of tablets of usual form of CA. Hence, of course, retard form of CA can maintain good, stable level of drug in the blood. Thus in this way, we can reduce incidence of episodes of ischaemia throughout 24 hours. In the past, in this respect, a lot of research had been done only on usual form of CA. Unfortunately, a little research work. had been done on retard form of CA regarding anti-ischaemic effect.

The purpose of this study is to provide scientific, documentary, proof of antianginal effect of retard verapamil, diltiazem & nifedipine. The following were the main task of our research:

1. To estimate the efficacy of retard verapamil, diltiazem & nifedipine.
2. To estimate anti-anginal effect.
3. To estimate tolerance of each drug
4. To estimate comparison of anti-anginal effects of three retard form calcium antagonist.

MATERIAL & METHODS

The efficacy of retard form CA has been estimated with the help of repeated Exercise Tolerance Tests (E.T.T.) Patients of stable angina pectoris, male

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(n=26) were studied in randomized, double blind manner. Diagnosis of stable angina pectoris was based on typical chest pain on exertion, ST segment depression on ECG during control ETT. All patients who have got typical chest pain of exertional angina pectoris of functional class II of classification of Canadian Cardiac Association.

Initially each patient followed by ETT without drugs, named as Control ETT; and mean ST segment depression was calculated in different leads. If ST segment depression was 1 mm or more, patient was found suitable for the study. Control ST segment depression of each patient was taken as base line. The basic method of our study was ETT, which was followed by BRUICE protocol. Also 24 hour Holter Monitoring was done in each patient before therapy & after therapy.

As we had no literature or materials providing or documenting the time of start of action of retard form of verapamil, diltiazem & nifedipine, we had done ETT, in first two patients, every two hourly. Thus ETT was done in first two patients after 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 hours of intake each retard form of CA. Then, it was found that anti-ischaemic effect was started after 4 hours, reaches its peak effect after 12 hours & moderately reduces after 18 hours in each retard form of CA. So onwards, we have done ETT after 4 hours, 12 hours & 18 hours in acute drug test. After acute drug tests, we have done short course therapy in each patients with 3-4 days of intake of each retard form of CA. In this therapy ETT was done after 4 hours & 12 hours. All patients received retard form of verapamil in 120 mg, 240 mg dose, retard diltiazem 90rng, 180 mg dose, retard nifedipine 20rng, 40 mg dose, with intervals of 3 days. During analysis of pharmacodynamical study following parameters were considered:

1. Pulse at rest, systolic BP at rest
2. Double product (D.P.) at rest& maximum.
3. Duration of ETT.
4. Maximal pulse at which ETT was terminated.
5. Time of start of chest discomfort & pain.
6 Time of start of ST segment depression
7. By comparing ST dep. of Control ETT & acute drug tests, % reduction of ST seg., is derived as Delta %---- Δ% ST seg. depression.

ST segment depression was calculated as mean ST segment depression in different leads. The calculated mean ST segment depression in control test was taken as base line and during therapy % reduction of ST segment was calculated, i.e., Δ% ST depression. The drug was considered effective if Δ% ST depression

$$\Delta\%\ \text{ST-depression} = \frac{\text{Baseline ST-depression} - \text{ST-depression after taking drug}}{\text{Basline ST-depression}} \times 100$$

was more then 30%.

RESULTS:

Results of Control ETT:

Mean pulse (n=26) at rest was 67.8± 2.6, systolic BP at rest was 139.1 ± 4.8, mean double product at rest was 9460.7±518.9, mean duration of ETT was 5.25±0.65 minutes, mean power in watts during ETT

Table 1
Results of 20 mg Retard Nifedipine after 4, 12 and 18 hour of ETT.

Parameters	Control	4 hour	12 hour	18 hours
Time of start of chest pain	2.66 ±0.44	3.77 ±0.77	2.4±0.44	1.75 ±0.5
Time of disapp.of chest pain	2.5±0.43	0.83 ±0.39	0.61 ±0.29	0.25 ±0.2
Δ%ST seg. depression	-	35.8±4.5	45.2±7.6	11.3 ±6.7
Resting pulse	68.1 ± 2.8	68.0 ± 3.6	69.0 ± 4.3	77.2 ± 8.8
Resting S. BY	138.4 ± 4.7	123.3 ± 3.7	129.5 ± 5.3	130.8 ± 5.5
Duration of test, mints.	5.40 ± 0.88	7.18 ± 0.76	6.2 ± 0.8	4.78 ± 0.4
Max. S.B.P.	174.5 ± 5.9	163.7 ± 5.08	164.4 ± 5.3	166.7 ± 9.4
Max. pulse at peak Test	112.5 ± 4.1-	109.6 ± 3.80	108.2 ± 3.70	108.0 ± 3.91
Max. D.P	19210.5 ± 1089.4	17545.7 ± 941.9	17842.6 ± 1014.7	17504.8 ± 1280.0

Table 2
Results of 240 mg of R verapamil after 4 hours, 12 hours, 18 hours of ETT (n=24)

Parameters	Control	4 hour	12 hour	18 hours
Time of start of chest pain, mints	2.7	2.7.9 ± 0.9	4.4 ± 0.3	3.4 ± 0.2
Time of disapp. of chest pain, mints	2.0	0.9 ± 0.4	1.2 ± 0.3	1.75 ± 0.84
Δ% ST seg. depression	-	58.6 ± 10.8	58.1 ± 8.8	46.5 ± 13.3
Resting pulse in minutes	63.6	61.3 ± 2.1	58.8 ± 2.5	60.3 ± 2.5
Resting S.B.P. mmHg	135.6	123.8 ± 3.3	116.7 ± 2.7	120.0 ± 2.4
Duration of ETT time, mints	4.8	7.6 ± 1.0	7.4 ± 0.9	6.5 ± 1.0
Max. S.B.P.	168.4	152.0 ± 3.7	139.3 ± 3.9 3.9	145.7 ± 4.4
Max. pulse at peak exercise	105	103.3 ± 3.0	97.6 ± 3.9	101.2 ± 4.6
Max. D.P.	17430.7	14939.6±751.2	13483.4± 11139	14334.3±1 1714.6

Table 3
Results of 180 mg of R diltiazem after 4 hours, 12 hours & 18 hours (n=16)

Parameters	Control	4 hour	12 hour	18 hours
Time of start of chest pain, mints	3.0	3.8±1.3	3.4±1.0	3.2±0.81
Time of dissapp. of chest pain, mints	2.3	1.2±0.5	1.1±0.3	1.5±0.5
Δ% ST seg. depression	-	65.1±13.5	41.9±14.1	30.4±8.6
Resting pulse	66.8	64.2±3.3	63.4±3.1	62.7±2.9
Resting S. BY	141.0	131.0±6.6	1.33.6±7.0	1.38.0±8.0
Duration of exercise time, mints	4.8	5.8±0.7	5.8±0.7	5.4±0.56
Max. S.B.P	175	158.7±9.1	162.0±8.1	166.5±12.3
Max. pulse	108.8	101.8±4.7	102.4±3.4	1.04.2±6.7
Max D.P	18468.7	15881.7± 1111.7	16588.8± 1130.5	17316±1250.1

was 58.77±7.7, mean maximum pulse during ETT was 111.7± 3.9, mean maximum systolic BP was 177.8±5.44, mean max. D.P. was 9417.2±1038.1 mean ST seg. depression at max., exercise was 1.6±0.5, mean time of start of chest pain was 2.62±0.5 minutes.

Results of Retard Nifedipine:
After taking of 20 mg of retard nifedipine, ETT was done after 4, 12, 18 hours, there was an increase in duration of exercise time without chest pain Mean Δ% ST seg. depression after 4 hours was 35.8, after 12 hours was 45.2, there was minimum effect after 18 hours. Table 1 shows mean reduction in systolic BP, pulse, D.P, etc. After 40 mg of retard nifedipine, Δ% ST seg. Depression after 4 hours was 41.6±15.9, after 12 hours was 39.2±1.1. So the effect of 40 mg of retard nifedipine is better than 20 mg. The increase in duration of exercise time was 26.3%. This effect continues over 12 hours. Max. systolic BP was reduced by 19 mmHg after 4 hours, same effect persist after 12 hours also.

Results of Retard Verapamil:
After the interval of 3-5 days, 120 mg of retard verapamil has been given & ETT was done after 4 , 12, 18 hours of intake. Δ% ST seg. depression was 36.4 % after 4 hour, 31 .4 % after 12 hours & 25 % after 18 hours. Resting S.B.P. reduced by 20.6% after 4 hour, 17.5% after 12 hours. Duration of exercise time was increased by 1.84 minutes after 4 hour, 1.6 minutes after 12 hours, 1.1 minutes after 18 hours.

But with 240 mg of retard verapamil anti- ischaemic effect was much more better than 120 mg. Table 2 shows Δ% ST seg. depression, ie, 58.6 % after 4 hour, 58.1% after 12 hours, & 46.5% after 18 hours of 240 mg of retard verapamil. Therefore, we can say that

240 mg of retard verapamil gives stable anti-ischaemic effect up to 18 hours.

Results of Retard Diltiazem:
Again after another interval of 3-5 days, 90 mg retard form of diltiazem was given, this shows good anti-ischaemic effect up to 12 hours only. Δ% ST seg. depression was 65.1% after 4 hours, 49.9 % after 12 hours & 16.4 % after 18 hours. Reduction in resting pulse was 5 % after 4 hours, 9.5% after 12 hours, reduction in resting systolic B.P. was by 16 % after 4 hours, 13 % after 12 hours. But duration of exercise time increased by 1.5 minutes after 4 & 12 hours.

With the use of 180 mg of retard diltiazem we have got an excellent anti-ischaemic effect as compare to 90 mg. Table 3 shows Δ%ST seg. depression with 180 mg. of retard diltiazem. After 4 hours A% St seg. depression was 65.1%, 41.9% after 12 hours, and 30.4 % after 18 hours.

DISCUSSION:

In the last two decades, CA has got increased popularity regarding treatments of cardio-vascular diseases. Since long time retard form of CA has got very important role in the management of arterial hypertension[1]. Diltiazem has been in used as anti-anginal drug but anti-anginal efficacy was not clear. With the use of retard forms of CA, we can reduce quantity of daily intake of tablets also, by this way we can maintain stable anti-ischaemic effect throughout 24 hours. By appropriate doses of retard form of CA. Up to now retard form of Diltiazem, verapamil, nifedipine are not in common use as anti-anginal drug. Therefore our study provide proof that retard forms of CA are potent anti-ischaemic agents.

All patients of ischaemic heart diseases have got limitations of exertion of work, when using normal form of CA. The retard verapamil, diltiazem, nifedipine, increase significantly limitation of exertions, significantly reduces frequency of chest pain, thus increasing good quality of life. Once or twice a day dose of retard CA offer patients good & comfortable life throughout 24 hours Although chest pain may occur at normal heart rate & at rest[2]. The majority of cerebrovascular accidents and ischaemic attacks occurs early in the morning or at night time. Because at night time , the level of drug in the blood reduces at its minimum. Therefore, there is need of such form of drug, e.g., retard form, which provides 24 hour protection of heart from ischaemic attacks, which is in fact, can reduce percentage of deaths. Earlier in European countries, research had been done on usual forms of beta blockers & calcium antagonists, i.e., verapamil, diltiazem, ifedipine et[3,4,5,7]. Their studies shows that the time of action & efficacy of usual form of CA are transient , short timed, from 2 to 6 hours. In this way, these agents can not maintain stable anti- anginal effect throughout 24 hours. Therefore, patients of ischaemic heart disease usually when taking usual forms of drugs, suffer from exertional angina pectoris most frequently. In our study, all three retard form of CA has proved good anti-ischaemic effect by significantly reducing ST seg. depression during ETT. The time of start of action of retard form of CA is 4-6 hours persist continuously up to 12- 18 hours.

We have used two doses of each retard form of CA in all patients. Nifedipine retard 20 mg shows good stable effect from 4 to 12 hours. Therefore, nifedipine retard 20 mg, may be given in patients of stable angina pectoris twice daily with confidence. When, we increased dose to 40 mg, the efficacy & anti-ischaemic effect has been increased, but unfortunately on the other hands, it shows few sides effects in majority of patients. The important side effects include palpitations, headache, flushing of face, uncomfortable feelings in the chest [20].

Verapamil retard in 120 mg dose, shows mild anti-anginal effects as compared to 240 mg[6.21]. There is clear & excellent anti-anginal effect by the use of 240 mg retard form of verapamil, which starts from 4 hours, and persists continuously up to 18 hours (Δ%ST =58.6%, 58.1%, 46.5%, after 4,12,18 hours respectively). The same research work had been done with a little difference by V .Subramanian in 1983, which also favors results of our study[6]. Hence retard verapamil in 240 mg. dose provide good benefit to patients with chronic angina pectoris, throughout 24 hours , without significant side effects. Now a days in Europe & USA, retard verapamil in high doses are in common use as anti-anginal agents [10,11,12,13,14,15]

Beside anti-anginal effects, CA also possesses a potent anti- effects, so it reduces chances of rupture of atheromatous plaques[8,9,22] and reduces chances of

acute ischaemic attacks, heart attacks etc. In this way mortality in those patients who are taking retard form of CA, will be less .

Since many years, diltiazem had been commonly prescribed by cardiologists as anti-anginal agent[16,17]. Retard form of CA is a good and potent anti-anginal drug[16,18,19]. Our work proves that retard diltiazem in 90 mg doses a good anti-anginal drug But the efficacy and anti-anginal potency has been increased significantly when we used 180 mg. of retard diltiazem. Our results shows that there is continuously stable anti-anginal effect from 4 hours to 18 hours (Δ% ST= 65.1, 41.9 %, & 30.4 % after 4, 12,18 hours resp.), without any significant side effects.

Comparative study been done also and it shows that the best anti-anginal agent is retard verapamil in 240 mg. dose. The second place taken by retard diltiazem in 180 mg dose. Nifedipine retard in 20 mg dose stands on third place. Nifedipine retard 40 mg is not good to recommend because of its side effects. In patients of mild to moderate angina pectoris retard verapamil in 240mg is recommended once daily only. If patient is hypertensive with mild to moderate angina pectoris, recommended dose is 240 mg twice daily. Retard diltiazem in 90 mg dose, is recommended for patients of mild to moderate angina pectoris once daily, but with moderate to severe angina pectoris 180 mg, once or twice daily is recommended. If patient is normotensive, 180 mg. of diltiazem twice daily does not reduce BP below normal values.

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