นิพนธ์ต้นฉบับ

Comparative efficacy of diltiazem and propranolol on treadmill exercise performance in chronic stable angina : a randomized crossover study

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The efficacy of diltiazem 180 mg/day and propranolol 120 mg/day in prolonging exercise end points in patients with chronic stable angina has been studied in this randomized crossover trial.

Twenty patients were divided into 2 groups after one week washout period. Then either 60 mg Diltiazem three times daily or 40 mg propranolol three times daily were given for a therapeutic period of 4 weeks. After this there was one week washout period again and the patients who had diltiazem before were changed over to propranolol and propranolol to diltiazem for another 4 weeks. Treadmill exercise stress tests were performed before and after 4 weeks therapeutic period of each durg. It was demonstrated that diltiazem significantly increased 1) time to onset of angina or fatigue if angina was eliminated 2) time to 1 mm. S-T segment depression and 3) time to terminate the exercise (all $P < 0.01$) while propranolol gave no significant improvement. As expected propranolol decreased both resting and exercise heart rate ($P < 0.01$) whereas diltiazem had no significant effect. There were no significant change of resting systolic, diastolic and exercise systolic, diastolic blood pressures by both drugs but propranolol decreased the double product ($P < 0.01$) more than diltiazem did ($P < 0.05$)

In conclusion diltiazem (180 mg.) improved exercise performance during the treadmill exercise stress test to a greater extent than did propranolol (120 mg.). No significant adverse effects or abnormal hematological findings were noted during the whole therapeutic periods of both drugs.

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ชมพูนุท อ่องจริต, ธนวัฒน์ ภาคีชีพ, วีณา ธารวณิชย์. การศึกษาประสิทธิผลเปรียบเทียบระหว่างยาดิลไทอาเซ็มกับโพรแพรนโนลอล โดยการออกกำลังกายด้วยการเดินบนสายพานในผู้ป่วยหัวใจขาดเลือดชนิดเรื้อรัง. จุฬาลงกรณ์เวชสาร 2533 มิถุนายน; 34(6): 441-448

รายงานนี้ได้ทำการศึกษาแบบ randomized crossover เปรียบเทียบการใช้ diltiazem 180 mg ต่อวัน กับการใช้ propanolol 120 mg ต่อวัน ในผู้ป่วยหัวใจขาดเลือดชนิดเรื้อรัง (chronic stable angina) เพื่อดูประสิทธิภาพในการออกกำลังของผู้ป่วยหลังจากได้รับยา ผู้ป่วยทั้งหมด 20 ราย กลุ่มแรก ได้รับยา diltiazem 60 mg วันละ 3 เวลา เป็นเวลา 4 สัปดาห์ และเปลี่ยนเป็น propranolol 40 mg วันละ 3 เวลา อีก 4 สัปดาห์ ส่วนกลุ่มที่สองได้รับ propranolol ก่อน 4 สัปดาห์ แล้วจึงเปลี่ยนเป็น diltazem อีก 4 สัปดาห์ โดยทั้งสองกลุ่มจะมีช่วง washout preriod ก่อนให้ยาตัวแรก และก่อนเปลี่ยนยาเป็นเวลาช่วงละ 1 สัปดาห์ ผลการศึกษาพบว่าผู้ป่วยได้รับยา diltiazem มีประสิทธิภาพในการเดินออกกำลังกายบนสายพานดีขึ้นอย่างมีนัยสำคัญ ($p < 0.01$) คือ 1) ช่วงเวลาที่เริ่มเจ็บหน้าอก หรือ fatigue หลังออกกำลังเพิ่มขึ้น 2) ช่วงเวลาออกกำลังจนพบมี S-T segment ลดต่ำลง > 1 มม. เพิ่มขึ้น 3) ระยะเวลาที่ออกกำลังกายเพิ่มขึ้น ส่วนผู้ป่วยที่ได้รับ propranolol ไม่พบมีการเปลี่ยนแปลงอย่างมีนัยสำคัญทางสถิติ ยกเว้นอัตราการเต้นของหัวใจขณะพักและขณะออกกำลังกายลดลงอย่างมีนัยสำคัญ ($p < 0.01$) ทั้ง diltiazem และ propranolol ในขนาดที่ใช้ในการศึกษานี้ ไม่พบว่ามีการเปลี่ยนแปลงของความดันเลือดขณะพักหรือช่วงออกกำลังกายอย่างมีนัยสำคัญทางสถิติ แต่ propranolol สามารถลด rate-pressure product (RPP) ($p < 0.01$) ได้มากกว่า diltiazem ($p < 0.05$) โดยสรุปแล้ว diltiazem (180 mg) สามารถเพิ่มประสิทธิภาพในการออกกำลังกายได้มากกว่า propranolol (120 mg) และไม่พบผลข้างเคียงในการใช้ยาทั้ง 2 ชนิด ตลอดระยะเวลาการศึกษานี้

Recent studies have shown the increasing evidence that diltiazem, one of the calcium slow channel blocking agents, is highly effective in the treatment of chronic stable angina as well as in Prinzmetal's angina which is due to coronary artery spasm,[1,5] while propranolol has been the mainstay in chronic stable angina for more than twenty years.[6-8] It is well established also that not all the patients with angina can tolerate betablockers especially when the patients also had another disorders such as obstructive lung disease, bradyarrhytmias, peripheral vascular disease, congestive heart failure, conduction disturbance etc.[9] Betablockers do not also relieve the pain of angina due to increased vasomotor tone or coronary spasm. From this aspect calcium-entry blokers such as diltizaem provides a promising and highly effective alternative to betablockers for the management of patients with chronic stable angina and fixed coronary artery disease.[10-13]

The purpose of this study was to compare the effect of oral diltiazem 60 mg three times daily and propranolol 40 mg. three times daily on exercise tolerance. Secondary objectives were to determine if there were any adverse effects and to assess the short-term safety of these two drugs.

Methods

Study Patients: patients with a classical history of stable angina on exertion having 5-15 anginal attacks per week were considered for entry into this study. Classical angina pain and at least 1 mm. horizontal or down-sloping ST segment depression must be demonstrated during the multistage exercise on a treadmill. Patients who had bad clinical congestive cardiac failure, conduction disturbance (sino-atrial and atrio- ventricular block more than 2nd degree) or bradycardia below 50 beats/minute or myocardial infarction during the past 6 months were excluded as were patients with valvular heart disease, chronic respiratary diseases including bronchial asthma and asthmatic bronchitis, hypothyroidism, hyperthyroidism, Raynaud disease or intermittent claudication. Twenty patients (14 men and 6 women, mean age 54.8 years, range 40-70) gave written informed consent to participate in this study. Six patients had coronary arteriography done confirming the presence of significant coronary artery disease signle-vessel disease in one, double-vessel disease in two and triple-vessel involvement in three. Three had doccumented myocardial infarction longer than 6 momths.

Experimental Protocol (Fig. 1): Each patient must stop all oral cardiac medications for one week of the observation period, only the use of sublingual nitroglycerin was permitted for angina pain, if needed. Then a four-week therapeutic period was started by either diltiazem 60 mg. three times daily or propranolol 40 mg. three times daily for 4 weeks respectively in cross-over open fashion. Another washout period of one week was plated between both therapeutic periods and only nitroglycerin was permitted for control of anginal attack in the same way as during the observation period. The twenty study patients were divided into 2 groups by randomization. Ten patients in Group 4 were given diltiazem first for the 4- week therapeutic period, followed by a one week washout period before the drug was switched over to propranolol, whereas ten patients in Group B were given propranolol first for 4 week, followed by 4 week of diltiazem after a one week washout period.

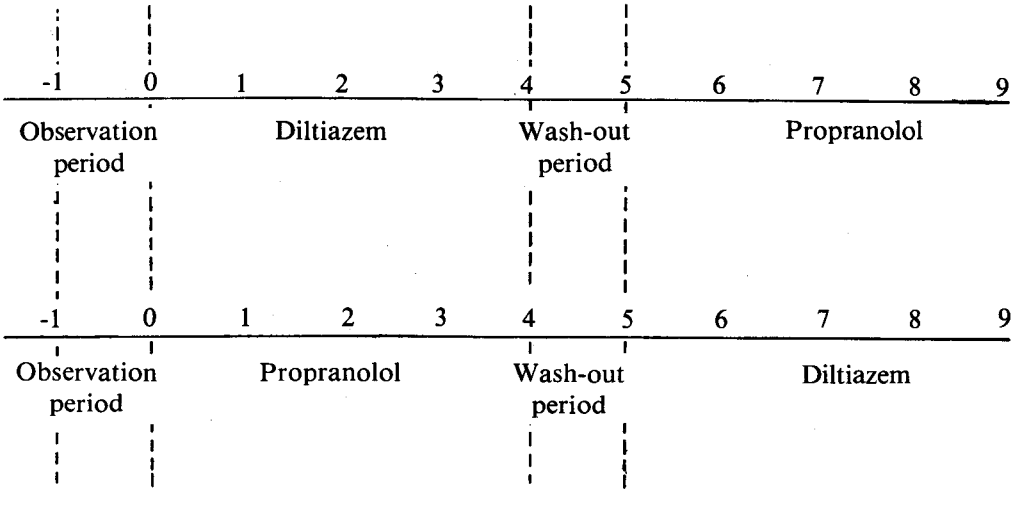


Figure 1. Schematic diagram outlining study protocol. There was 1 week observation period followed by 4 week therapeutic periods which patients were randomly assigned to receive diltiazem or propranolol. Then there was 1 week wash-out period and the medication was cross-over for another 4 week therapeutic period.

Exercise Treadmill Protocol: Exercise treadmill tests were performed with Bruce protocol by every patient at the beginning and end of each therapeutic period, after a 3 hours fast and 2-4 hours of diltiazem or propranolol administration. All patients were to exercise until the onset of both diagnostic ischemic ST segment depression and angina pectoris. Moderately severs angina pain, or severe fatigue if angina was eliminated were used as end points for termination of the exercise tests, so that all patients were exercised to symptom-limited maximal effort and not to a percentage of age-predicted heart rate or a fixed magnitude of ST depression which was in contrast to some other studies. Lead II, aVF and V5 were monitored continuously during exercise and recovery periods. Heart rate and blood pressure by cuff sphygmomanometer were measured after each minute and during recovery.

For each treadmill test, three end points were assessed: 1) time to onset of angina or fatigue if angina was eliminated **2)** time to 1 mm. ST depression **3)** time to terminate the exercise. Changes in heart rate, electrocardiogram, blood pressure and rate-pressure (maximum heart rate X maximum systolic blood pressure X 10^{-2}) were also assessed. Data were analysed at rest, at onset of ST depression, at onset of angina, and during maximal exercise.

Clinical Observation: The frequency of anginal attacks were checked at the beginning and every 2 weeks for each therapeutic period. Also the total numbers of nitroglycerin tablets taken were checked at the same time. Physical examinations especially blood pressure and heart rate were also noted. The patients were questioned specifically about adverse effects and reliability of dose taking, and pill counts were done to ensure compliance.

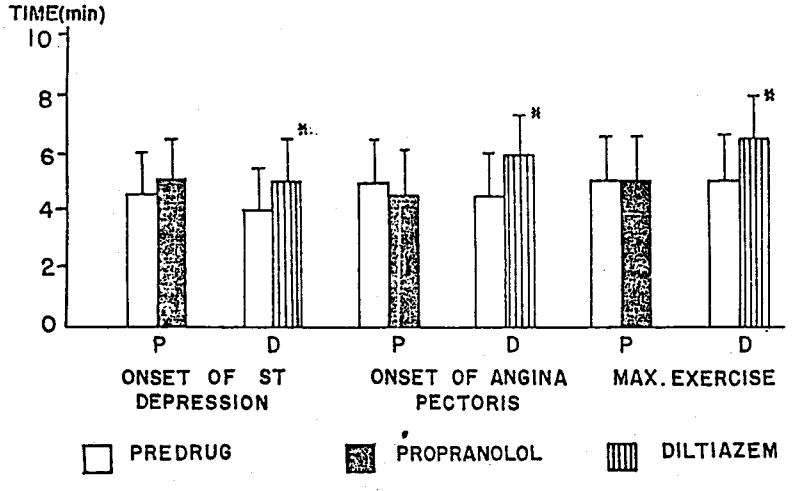
Laboratory Protocol: Blood chemistry profile included blood sugar, blood urea nitrogen, creatinine, uric acid, electrolytes, cholesterol, triglyceride, liver function tests consisting of alkaline phosphatase, SGOT, SGPT, were obtained together with complete blood count at the beginning and end of each therapeutic period. Urine was also obtained for urinalysis at the same time as chemistry profile.

Statistics: Data were expressed as mean $\pm$ S.D. and $p<0.05$ was considered significant. Statistical comparisions were made using a t test of paired samples.

Results

Twenty-four patients were entered into the study. Four were discharged from the protocol : 2 because of failure of compliance, one because she did not like many treadmill tests and one because of inconvenience to the patient. All twenty patients (14 male and 6 females) completed the study protocol without any complication or intolerable adverse effects.

The average numbers of anginal attacks during the pretreatment and therapeutic periods decreased from 7 ± 5 episodes/week to 2 ± 1 by diltiazem ($p<0.06$) and 8 ± 5 episodes/week to 4 ± 3 by propranolol ($p=NS$). The number of sublingual nitroglycerin consumpition per week showed no significant differences between diltiazem and propranolol during the therapeutic periods.



* Statistical significance at $\alpha = 0.01$

Figure 2. Total Exercise Duration By Treatment Study of Both Groups (n = 40)

Excrcise Tolerance and ischemic electrocardiographic responses. Diltiazem produced a highly significant effect by prolonging three end points of the exercise ($p<0.01$):- time to onset of ST depression, time to onset of angina pectoris and maximal or total exercise duration (Fig. 2) The ST segment depression occured at 4.3 ±2.5 mm. and during propranolol 4.8 ±3.1 mm. during diltiazem therapy. During the predrug period of propranolol ST segment depression 4.3±2.5 m. and during propranolol treatment. at 4.8±2.7 m. which should no statistical significance.

The time of onset of angina before and after drug was 4.8 ±2.3 vs 6.2 ±2.7 m. for diltiazem and 5.2±2.3 vs 5.1±2.6 for propranolol. This time was actually decreased by propranolol in our study because five patients had no real angina pain but severe fatigue was observed, and owing to this symptom exercise was impaired instead of improved. The maximal exercise time of predrug vs drug was also significantly improved by diltiazem 5.1±2.3 m. vs 6.3±2.5 m. Changes in this time by propranolol therapy did not attain significance 5.4±2.2 vs 5.4±2.4 m.

For both drugs the ST segment was less depressed but without statistical significance, at the onset of angina and during maximal exercise.

Hemodynamic Response

Effect of therapy on rest variables, resting heart rate and blood pressure, both systolic and diastolic, immediately before treadmill exercise were not affected by diltiazmen in both groups A & B (Table 1 & 2). As expected resting heart rate was decreased significantly by propranolol in Group B from 86.1±15.4 to 67.4±8.6 bpm ($p<0.01$) but was not significant by changed in Group A (from 89±23.1 to 78±12.2 bpm). Rate-pressure products at rest were decreased significantly ($p<0.05$) by both diltiazem and propranolol in Group A and decreased more significantly ($p < 0.01$) by propranolol in Group B.

Table 1. Effect of Treatment on Rest and Exercise Variables in Patients Group A.

	Diltiazem (n=20)		Propranolol (n=20)	
	Pre	Post	Pre	Post
Resting Variables				
HR (bpm)	77.9±10.5	73.8±14.2	89.1±23.1	78±12.2
SBP (mm.Hg.)	153±24.9	137±6.7	140±18.3	133.8±17.6
DBP (mm.Hg.)	97±10.6	89±3.2	89±8.8	87±9.5
RPP ($HR \times SBP \times 10^{-2}$)	119.5±26.1	102.4±20.5*	125.5±37.6	92.8±14.5*
Exercise Variables				
1. Onset of ST Depression :				
HR	141.7±17.9	135±15.6	140±17.8	105.2±20.7
SBP	169±23.8	164.4±23.5	153±22.1	149±18.5
DBP	101±13.7	100±7.1	94±8.4	95±5.3
RPP	240.9±52.3	225.8±56.9	215.9±53.6	157.5±42.3
2. Onset of Angina :				
HR	145±15.3	141.7±17.7	146±14.5	107.3±22.6
SBP	158.5±23.7	170±21.1	154±22.2	150±17.6
DBP	102±13.2	101±5.7	95±8.5	96±5.2
RPP	249.3±47.5	226±52.5	227.4±56.9	163.3±48.1
3. Maximal Exercise :				
HR	146.7±13.9	143.2±16.1	146.6±13.7	110±22.6
SBP	172±23.5	171±20.8	154±22.2	150±17.6
DBP	102±13.2	101±5.7	95±8.5	96±5.2
RPP	252.4±47.1	229.8±50.7	227.7±52.6	165.8±45.6
Exercise Tolerance (Time)				
Onset of ST Depression	3.6±2.5	4.8±2.6**	4.4±2.8	4.8±2.7
Onset of Angina	4.2±2.3	5.9±2.5**	5.3±2.4	4.9±2.7
Maximal Exercise	4.7±2.2	6.1±2.2**	5.5±2.2	5.5±2.3
ST Segment Depression (m.m.)				
Onset of Angina	1.0±0.4	0.8±0.5	1.2±0.6	1.0±0.5
Maximal Exercise	1.0±0.5	0.9±0.7	1.4±0.6	1.1±0.7

* Statistical significance at $\alpha = 0.05$
** Statistical significance at $\alpha = 0.01$

Table 2. Effect of Treatment on Rest and Exercise Variables in Patients Group B.

	Propranolol (n=20)		Diltiazem (n=20)	
	Pre	Post	Pre	Post
Resting Variables				
HR (bpm)	86.1±15.4	67.4±8.6**	88.6±11.7	81.6±14.2
SBP (mm.Hg.)	137±13.4	130.4±18.1	133±18.9	133±13.4
DBP (mm.Hg.)	90±6.7	87.4±9.7	89±9.9	87±6.7
RPP (HR×SBP×10^{-2})	117.1±18.4	88.3±19.2	**117.7±22.9	106.9±15.7
Exercise Variables				
1. Onset of ST Depression :				
HR	141.1±15	114.1±10.8	139.9±18.1	134.8±17.0
SBP	147.4±17.9	137.8±19.4	141±14.5	146±14.3
DBP	97±8.2	92±6.4	95±8.5	96±5.2
RPP	208.2±35.4	156.8±23.9	196.8±29.7	195.9±25.3
2. Onset of Angina :				
HR	145.6±18.4	120.5±13.9	150.2±17.7	146.3±20.1
SBP	151.4±19.2	141.4±19.6	144±16.5	154±17.1
DBP	98±9.2	96±7.0	98±7.9	108±28.9
RPP	220±31.6	167.7±27.6	215.1±27.0	224.4±34.5
3. Maximal Exercise :				
HR	147.4±15.6	120.5±13.9	151.1±16.2	148.3±17.2
SBP	151.4±19.2	141.4±19.6	144±16.5	158±26.2
DBP	98±9.2	96±7.0	98±7.9	99±5.7
RPP	222.1±28.6	167.7±27.6	261.8±27.7	233.3±39.1
Exercise Tolerance (Time)				
Onset of ST Depression	4.1±2.2	4.7±2.7	4.0±2.8	4.8±3.6
Onset of Angina	5.0±2.2	5.3±2.5	5.4±2.3	6.4±2.8*
Maximal Exercise	5.2±2.1	5.3±2.5	5.4±2.3	6.5±2.8*
ST Segment Depression (m.m.)				
Onset of Angina	1.3±0.4	1.2±0.7	1.8±0.8	1.4±1.1
Maximal Exercise	1.3±0.4	1.2±0.7	2.2±0.8	1.5±1.1

* Statistical significance at $\alpha = 0.05$
** Statistical significance at $\alpha = 0.01$

Effect of therapy exercise variables: Heart rate, systolic and diastolic blood pressures including the rate-pressure product during exercise performance at onset of ST depression, at onset of angina and at maximal exercise showed changes which did not reach significance for both drugs. No remarkable abnormalities of blood chemistry and blood counts were present.

Adverse effects: Two patients complained of palpitation after the first few days of diltiazem administration but this complaint disappeared as the trial went on without interruption. Four patients suffered from easy fatigibility and muscular weakness with propranolol therapy but they could tolerate the drug until their therapeutic period was complete without the need for withdrawal.

Discussion

The efficacy of diltiazem in this study was very satisfactory in the treatment of chronic stable angina though the doses given were low when compared to studies using high doses of 360 mg/day,[14-15] and 240 mg/day[16-19] in Japan and United states. Despite the rather low dose in this study improvement in exercise performance could be obviously demonstrated between the predrug and drug periods and also between diltiazem 180 mg/day and propranolol 120 mg/day.

Our data did not show a significant reduction in resting and exercise heart rate after diltiazem therapy as Koiwaya et al[20] demonstrated a 144 sec improvement in time to ST depression, 150 sec improvement in time to onset of angina pectoris and 150 sec improvement in time to peak exercise by using 90 mg dose of diltiazem and Wagniart et al[21] demonstrated 170 second improvement in time to onset of ST segment depression and 105 sec improvement in time to peak exercise. Our data are comparable to the improvement mentioned but to a lesser extend. We have found that the time to ST

segment depression increased by 60 sec., the time to angina pectoris by 64 sec and the time to maximal exercise by 62 sec.

In contrast propranolol exerted variable, and generally insignificant effects on exercise performance in our study. The time to onset of ST depression was increased but did not reach significance as well as the time of total exercise. The result of time to onset of angina or fatigue if angina was eliminated was even shorter by propranolol therapy because even though the study patients had no pain, severe fatigue was their main exercise problem. Our result was different from the study reported by Anderson et al[22] in which the exercise duration was increased 16% and exercise double product was substantially reduced, indicating effeect. There was some increase in exercise duration following propranolol administration but this did not reach significance and the rate-pressure product was not significantly changed. The patients with old myocardial infarction were the ones who had exercise tolerance decreased after propranolol therapy. This indicated significant or severe left ventricular dysfunction in these patients and the peak exercise tolerance was most frequently limited by fatigue, the same as reported by Hang et al.[23]

On the other hand, W.E. Strauss et al.[24] reported that combined diltiazem-propranolol therapy demonstrated a further improvement in rate of angina attack and nitrogen consumption as well as exercise duration without significant adverse reaction except for one case of congestive heart failure.

Therapeutic implications: In summary, diltiazem in daily dose of 180 mg appeared to be a safe and effective therapy for chronic stable angian compared with propranolol in daily dose of 120 mg. Diltiazem increased exercise performance more than propranolol did. there was no significant adverse effect in the study group. In addition to the efficacy of diltiazem on angian pectoris, R. Roberts et al.[25] concluded that diltiazem was effective in preventing early reinfarction and severe angina after non-Q-wave infarction and it was also safe and generally well tolerated, and R.A. Q'Roourke[26] and P.E. Pool et al[27] reported the efficacy of diltiazem on systemic hypertension complicated by coronary heart disease and systemic hypertension as monotherapies, respectively.

Theirs as well as our study suggest that diltiazem will be useful for not only angina pectoris but also other cardiovascular diseases such as myocardial infarction and hypertension associated with ischemic heart disease, as a calcium antagonist with cardioprotection.

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