Tiapamil dose ranging study on exercise performance in patients with exercise induced angina and coronary artery disease.

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In a double blind study, the effects of 4 single different doses of a new calcium antagonist tiapamil (RO 11-1781) on exercise performance were evaluated in 10 patients with stable angina, positive exercise ECG's and proven coronary artery disease. Maximal treadmill exercise ECG's were performed before tiapamil (control) and after oral 200 mg, 400 mg, 600 mg and 800 mg tiapamil or randomized matching placebo. Exercise duration, minimum work load provoking angina and work load inducing 1 mm ST depression were similar during control and placebo periods. Exercise duration improved from 299 ± 40 sec (mean ± SEM) after placebo to 399 ± 49 sec post-tiapamil 600 mg, $p < 0.05$; and to 416 ± 49 sec post-tiapamil 800 mg, $p < 0.05$. The maximal heart rates, systolic blood pressures and double products post-tiapamil were similar to both control and placebo results. Eight of the 10 patients remained free of angina post-tiapamil 600 mg and tiapamil 800 mg, at work loads which induced angina during the control tests and after placebo. The improvement in effort tolerance was associated with a significant increase in the exercise time for the earliest induction of 1 mm ST-segment depression, from 202 ± 35 sec post-placebo to 300 ± 48 sec post-tiapamil 600 mg, $p < 0.05$; and to 272 ± 51 sec for 9 patients post-tiapamil 800 mg, $p < 0.05$. One additional patient had normalization of the control exercise ECG ischaemic changes post-tiapamil 800 mg. Three of the 10 patients had transient mild dizziness or blurred vision and were possible side effects occurring after tiapamil. Tiapamil is highly effective for the relief of exercise induced angina in patients with stable angina and significantly improves exercise performance.

Calcium antagonist drugs have been successfully used in the treatment of patients with symptomatic ischaemic heart disease. The action of calcium in excitation-contraction coupling in cardiac and arteriolar musculature is specifically inhibited by calcium antagonist drugs. There is laboratory evidence in isolated smooth muscle preparations and the experimental animal to show that tiapamil (Ro 11-1781) dilates peripheral resistance and coronary vessels [1,2]. Tiapamil in single doses given intravenously (1 mg/ kg) or 500 mg orally has been previously shown to increase exercise tolerance and improve myocardial perfusion in patients with exertional angina [3].

The aims of the study are: 1) to determine the efficacy of varying doses of tiapamil in preventing exercise induced angina. A further analysis will be made to assess the relationship between efficacy of tiapamil on exercise induced angina and plasma levels; 2) to monitor any adverse effects with varying doses of tiapamil.

Patients and methods

The study group comprised 10 patients with stable angina who had documented, severe (greater than 70% luminal narrowing), fixed obstructive coronary artery disease with reproducible exercise induced angina, accompanied by at least 1 mm flat or downsloping ST segment depression for at least 80 ms after the J point.

Patients with unstable angina, valvular heart disease, known left main coronary artery stenosis, cardiac failure, abnormal renal or liver function tests, sick sinus syndrome, bundle branch block, atrioven-

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tricular block and patients requiring other anti-anginal drugs or digitalis were excluded from this study.

The study was double blind and placebo controlled. Adrenergic beta blocking drugs and calcium antagonist drugs were ceased for at least 72 hours prior to tiapamil or placebo. No patient had occasion to take nitrates or nitroglycerin on the day of each test. To minimize severity of possible side effects after tiapamil patients received increasing doses of either 200 mg, 400mg, 600mg and 800mg tiapamil. In addition, patients received a randomized matching placebo. A minimum interval of 24 hours separated each drug or placebo administration. Because the variable tiapamil doses were not randomized, an exercise test was performed 30 minutes before drug or placebo administration as a control test to assess any possible drug or training effect.

Each study consisted an initial treadmill exercise ECG and a repeat study 2 hours 30 minutes after drug or placebo administration, according to the modified Bruce protocol [4].

During the period of exercise continuous ECG monitoring was performed and a 12 lead ECG was recorded every minute. After the cessation of exercise, ECG's were performed every minute for a minimum of 90 minutes or for a longer period if ECG ST segments had not returned to pre-exercise levels. Blood pressure was recorded every 3 minutes. Identical 12 lead ECG electrode placement was ensured on successive tests by crystal violet skin marking.

The patients exercised until the onset of moderate angina or fatigue which would normally preclude them from continuing exercise, or the development of hypotension (a sustained decrease of 10 mmHg or more in the systolic blood pressure).

The following parameters were measured: 1) exercise duration (ex time); 2) work load in Mets (ex load) [5]; 3) the duration of exercise to the onset of angina (angina onset); 4) the time from the onset of angina to relief of angina post-exercise (angina duration).

Exercise ECG's were interpreted by 2 observers according to the criteria of the American Heart Association [6]. The exercise ECG was considered positive for myocardial ischaemia if there was exercise induced 1 mm or greater, horizontal or down sloping, ST segment depression for at least 80 ms after the J point in any lead. The following parameters were measured: 1) maximum degree in mm of ST segment depression at 80 ms after the J point in a single ECG lead occurring at peak exercise (ST fall); 2) time to the onset of exercise induced 1 mm ST segment depression in an identical single ECG lead during control and post-tiapamil tests (onset 1mm ST fall); 3) time to the onset of exercise induced maximum severity of ST segment depression in an identical single lead during control and post-tiapamil tests (onset ST fall); 4) time for ST segments in all 12 leads of the ECG to return to pre-exercise levels after exercise (ST return normal).

At two and a half hours after each drug administration, adverse reactions were elicited from the patient and in addition the patient was specifically questioned concerning known adverse reactions to other calcium antagonists. Reactions were graded mild, moderate or severe. Severe reactions were those which precluded the patient continuing the trial. Mild reactions were those which were considered a minor nuisance by the patient.

The Student's paired t test was used for statistical analysis and a difference of $p < 0.05$ was considered significant. To assess the efficacy of tiapamil the post-tiapamil results were compared with its respective control test and with the results after placebo. To assess whether there was any training effect on repeated exercise during this protocol, blood pressure and heart rate responses to maximal exercise, exercise duration, time to onset of angina, duration of angina and ST segment changes were compared for the five control periods.

The patients comprised 10 males and 1 female, with a mean age of 46 (range 35 to 62) years, who commenced the trial. Patient 2 commenced the trial and was withdrawn from the study because of angiographically documented severe left main coronary construction at the time of study. Three patients smoked cigarettes during the trial and one patient had ceased smoking 1 month prior to the trial. Three patients had mild hypertension with diastolic blood pressures ranging from 95 to 110 mmHg.

Results

Blood pressure and heart rate response - The rest and exercise heart rates (HR), systolic and diastolic blood pressures (BP) and double products (DP = HR x systolic BP / 100).

There were no significant differences in rest or peak exercise HR, systolic BP or double products in comparing placebo and post-tiapamil values. During individual tests there was an expected significant increase in HR, systolic BP and double products from rest to exercise. Three patients with mild diastolic hypertension became normotensive (diastolic BP less than 95 mmHg) after tiapamil 600 mg and 800 Mg.

Exercise tolerance - The duration of exercise increased significantly from 299 ± 40 sec (mean ± standard error of the mean) for the placebo period to 342 ± 44 see post-tiapamil 400 mg ($p < 0.05$); to 399 ± 49 sec post-tiapamil 600 mg ($p < 0.025$); and to 416 ± 49 sec post-tiapamil 800 mg ($p < 0.005$). The improvement in exercise tolerance after tiapamil 600 mg or 800 mg doses was significant when compared with 295 ± 38 sec post-tiapamil 200 mg ($p < 0.005$) and 342 ± 44 sec post-tiapamil 400 mg ($p < 0.05$).

Work load, as assessed in METS, increased from 6.0 ± 0.4 after placebo to 7.0 ± 0.5 post-tiapamil 600

mg, $p < 0.01$; and to 7.1 ± 0.5 post-tiapamil 800 mg, $p < 0.01$, There was no significant improvement after 200 mg and 400 mg tiapamil. There was no placebo response observed in comparing control and placebo results. In addition there were no significant changes in control and placebo results. This suggests a training effect did not occur during the successive exercise tests.

Threshold and duration of angina - On comparison with placebo and control tests, the time to onset of angina was significantly increased after 400 mg, 600 mg and 800 mg tiapamil ($p < 0.025$). Patients 4 and 6 had complete relief of angina at peak exercise after 600 mg and patients 5 and 6 had complete relief after tiapamil 800 mg. These patients were not included in this statistical comparison. However the complete relief of angina in these patients was associated with an increased exercise tolerance. The total duration of angina (the time from the onset of angina during exercise to complete relief after ceasing exercise) was not significantly different after tiapamil.

Electrocardiographic results - After tiapamil 600 mg and 800 mg the patients were able to achieve an additional workload and this was associated with ECG evidence of delays in the onset of initial ischaemia and in the onset of maximal ischaemia. The time to onset of maximum ST segment depression, as evidence of maximum ischaemia, was significantly increased from 274 ± 34 see post-placebo to 368 ± 51 sec post-tiapamil 600 mg ($p < 0.05$) and to 379 ± 51 see post-tiapamil 800 mg ($p < 0.025$). There were no significant differences between placebo and tiapamil 200 mg and 400 mg. Tiapamil 800 mg significantly increased the time of onset of maximum ST depression when compared with tiapamil 400 mg, 309 ± 40 see ($p < 0.05$).

The time to onset of 1 mm ST segment depression, as evidence of initial ischaemia, increased significantly from 202 ± 35 sec post-placebo to 300 ± 48 sec post-tiapamil 600 mg ($p < 0.05$); and to 272 ± 51 sec post-tiapamil 800 mg ($p < 0.05$). Patient 6 could not be included in the tiapamil 800 mg comparison as exercise induced 1 mm ST depression did not occur at all. Tiapamil 600 mg and 800 mg significantly increased the exercise duration for the onset of 1 mm ST depression when compared with post-tiapamil 400 mg, 222 ± 34 sec ($p < 0.05$) and 210 31 sec post-tiapamil 600 mg ($p < 0.05$).

In comparing the times taken for ST segment depression to return to pre-exercise levels, tiapamil 800 mg was the only dose that significantly decreased this time. There was a decrease from 210 -h 34 see after the placebo to 120 ± 34 see post-tiapamil 800 mg, $p < 0.05$.

Adverse reactions - Four patients noticed side effects after tiapamil and no adverse reactions after placebo. Patient 3 experienced symptoms of blurring of vision and malaise of moderate severity after tiapamil 800 mg. These symptoms persisted for 4 hours.

Patient 5 complained of mild lightheadedness of 30 min duration following only 400 mg tiapamil and it is possible that the effect was not drug related. Patients 8 and 11 complained of mild dizziness and blurring of vision after 600 mg and 800 mg tiapamil. These side effects persisted for 3 and 1 hours respectively. No side effect was associated with hypotension (systolic blood pressure less than 100 mg Hg) or with arrhythmias.

Discussion

In a previous clinical study, oral dosing with tiapamil (500 mg) has been shown to be an effective anti-anginal drug [3]. The aim of this study was to investigate the effects of different doses of tiapamil on exercise tolerance and exertional angina. Seven of the 10 patients had an increase in effort tolerance and alleviation of their angina post-tiapamil 800 mg. At higher work loads tiapamil 800 mg delayed the onset of exercise induced ST segment abnormalities and reduced the duration of continuing ischaemia after exercise. In addition, after tiapamil 600 mg, 6 of the 10 patients had similar changes without a reduction in the duration of ischaemia after exercise. However at the new peak level of exercise there was no significant decrease in the severity of angina or ischaemia, as evidenced by maximum ST segment depression in a single lead, after tiapamil. These antianginal effects did not occur after lower doses of tiapamil and no placebo effect was observed. In comparing successive control tests, there was no evidence of a training effect and therefore anti-anginal effects can be inferred post-tiapamil.

There was a decrease in the resting systolic blood pressure post-tiapamil and 3 patients with diastolic hypertension became normotensive. These changes were not associated with symptoms. During exercise, the post-tiapamil peak double products, heart rates and systolic blood pressures were comparable with those for the control and placebo tests. These changes occurred at an increased work load after tiapamil and indicated that tiapamil's anti-anginal effect is independent of heart rate and blood pressure responses to maximal exercise. Although peripheral and coronary vasodilatation have been postulated for tiapamil's mechanism of action for the relief of exertional angina, the mechanism of action of tiapamil can not be inferred from this study.

Side effects were relatively common (3 of 10 patients) after tiapamil 800 mg. Although they were generally mild in severity, 1 of the 10 patients had moderate side effects which lasted approximately 6 hours and would have prevented long-term drug administration. Only 1 of the 10 patients had side effects after 600 mg tiapamil and this single dosage was well tolerated by the patients studied. The mild headache noticed in patient 5 after tiapamil 400 mg alone was probably not drug related and no placebo response was found.

In conclusion: 1) tiapamil 600 mg and 800 mg are effective at 2 to 3 hours in preventing exercise induced angina and improving exercise tolerance in this selected group of patients with stable angina. Tiapamil 800 mg and 600 mg were significantly more effective than tiapamil 200 mg and 400 mg. Although tiapamil 800 mg was associated with the most improvement, it was not significantly greater than tiapamil 600 mg; 2) transient side effects of blurring of vision and dizziness occurred in 3 patients after tiapamil 800 mg. They were mild in severity and of brief duration in 2 patients and of moderate severity in 1 patient. They occurred independently of changes in blood pressure and heart rate. Tiapamil 600 mg was better tolerated than tiapamil 800 mg; 3) tiapamil 600 mg, in a single dose, is a highly effective for the relief of exertional angina at 2 to 3 hours after administration with a low incidence of mild side effects.

Resumo

Num estudo duplamente cego, os efeitos de quatro doses distintas, administradas em uma única tomada de um novo antagonista do cálcio (tiapamil - RO 11-1781), sobre o desempenho durante o esforço foram avaliados em 10 pacientes com angina estável, eletrocardiograma de esforço alterado e coronariopatia comprovada. O eletrocardiograma após esforço máximo foi obtido antes de tiapamil (controle) e depois de 200 mg, 400 mg, 600 mg e 800 mg de tiapamil oral ou placebo, segundo determinação aleatória.

A tolerância ao exercício, a carga mínima desencadeante de angina e a carga determinante de infradesnivelamento de ST de 1 mm foram semelhantes durante os períodos de controle e sob uso de placebo. A tolerância ao exercício melhorou de 299 ± 40 s após placebo para 399 ± 49 s após 600 mg do tiapamil ($p < 0,05$) e para 416 ± 49 s após 800 mg de tiapamil ($p < 0,05$). A freqüência cardíaca máxima, a pressão arterial sistólica e o duplo produto após tiapamil foram semelhantes tanto aos registrados após a fase de controle como após o uso de placebo. Oito de 10 pacientes não apresentaram angina após 600 mg e 800 mg de tiapamil perante cargas que induziram angina durante os períodos de controle e de uso de placebo. A melhora da tolerância ao exercício associou-se a significativo aumento no tempo de exercício para que comparecesse um infradesnivelamento de ST de 1 mm, de 202 ± 35 s após placebo para 300 ± 48 s após 600 mg de tiapamil ($p < 0,05$) e para 272 ± 51 s em 9 pacientes após 800 mg de tiapamil ($p <,0,05$). Após 800 mg de tiapamil, um outro paciente normalizou o ECG previamente com alterações isquêmicas. Três de 10 pacientes apresentaram tonturas moderadas transitórias e visão borrada, que podem ser efeitos indesejáveis de tiapamil. Tiapamil é altamente eficaz para aliviar a angina induzida pelo esforço em pacientes com angina estável e melhora significativamente o desempenho no exercício.

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