ANTIARRHYTHMIC EFFECTS OF TIMOLOL IN PATIENTS WITH VENTRICULAR ARRHYTHMIAS

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The purpose al this study was to determine the antiarrhythmic affects of timolol maleate in patients with frequent and multifocal ventricular premature depolarizations (VPDs), couplets and episodes of non-sustained ventricular tachycardia (VT).

Timolol maleate (titrated from 10 to 30 mg b.i.d.) was given to 31 patients in a multiclinic double-blind, placebocontrolled crossover study. The primary assessment of efficacy for ventricular arrhythmias was based on 24 h Holter monitoring while the degree of beta-blockade was determined by the decrease in peak exercise heart rate. Administration of timolol maleate caused reductions of: 36% in the exercise heart rate, 39% in VPDs/24h (from 383 ± 80 to 232 ± 63, $p < .05$), 81% in couplets (from 239 ± 84 to 44 ± 17, $p < .05$), and 83% in the incidence of more than one VT event during the 24 hours of monitoring (from 46% to 8%, $p < .01$). This suggests that timolol maleate, given in a dose that produces beta-blockade, is a promising agent for the treatment of frequent and multifocal VPDs, couplets and episodes of nonsustained VT.

Arq. Bras. Cardiol. 51/4: 359-364—Outubro 1988

Ventricular arrhythmias [i.e., ventricular premature depolarizations (VPDs), couplets and ventricular tachycardia (VT)], are frequently encountered in patients with coronary artery disease[1,2]. The frequency morphology and site of VPDs in the cardiac cycle are variables used to identify patients with a high risk for sudden death[3, 4].

Couplets are precursors of malignant arrhythmias such as ventricular tachycardia, which can potentially degenerate to fatal ventricular fibrillations. These ventricular arrhythmias are very common in patients with coronary artery disease and contribute to the high mortality rate in the first year following acute myocardial infarction[5,6]. Various anti-arrthythmic agents (i.e., quinidine, procainamide and disopyramide), are widely used to treat ventricular arrhythmias following myocardial infarction, although a beneficial effect of this therapy in reducing mortality has never been demonstrated[7]. Beta-blocking agents, on the other hand, have shown to be effective in reducing mortality after myocardial infarctions. Precisely why betablockers are beneficial in these patiens needs further investigation.

The purpose of this study was to evaluate the antiarrhythmic effects of timolol maleate, a non-selective beta-blocker without intrinsic sympathomimetic activity, in patients with ventricular arrhythmias.

PATIENTS AND METHODS

Patients Population—The population consisted of 31 outpatients (20 male, 11 female), between the ages of 40 and 77 years, who demonstrated at least 300 VPDs in a 24-hour Holter monitoring period. The duration of the ventricular arrhythmias ranged from 1 month to 50 years. Patients with life-threatening arrhythmias (sustained VT and/or episodes of ventricular fibrillation), congestive heart failure or hemodynamically significant valvular heart disease; A-V conduction defect or WPW syndrome; secondary or malignant hypertension; diabetes; or a history of recent stroke or myocardial infarction were excluded from the study. However, all patients had chronic coronary artery disease and 26 out of the 31 had a history of previous myocardial infarction.

Study design (fig. 1)—This was a multiclinic, double-blind, placebo-controlled, crossover study consisting of a two-week baseline placebo washout period, a two to six-week initial treatment period (Period D, a two-week interim washout period, and another two to six-week treatment period (Period II). All anti-arrhythmic therapy was discontinued at the start of the baseline period. Patients had a complete physical examination, laboratory screening, urinalysis, an electrocardiogram and chest x-ray at the initial visit.Twen-

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ty-four hour Holter monitoring was performed on days 7 and 14 of both washout periods and at the end of each treatment period. An exercise tolerance test, using a standard Bruce protocol, was performed at the end of the washout and each treatment period. Since beta-blocker therapy reduces the heart rate, the frequency of ventricular arrhythmias was analyzed over 24 hours and also adjusted for the number of heart beats and presented per 1000 heart beats. The analysis of ventricular arrhythmias was performed in the final week of each treatment period. The frequency of ventricular arrhythmias was calculated by the hour, adjusted for the number of heart beats, and separately tabulated for daytime and nighttime. Additionally, patients were also evaluated for hours at "risk", where risk was defined as 30 or more VPDs an hour. Exercise testing was performed using a standard Bruce protocol. Heart rate and blood pressure were measured only at the conclusion of the exercise test. Since patients exercised for varying lengths of time during the two treatment periods, the effects on blood pressure and heart rate could no be compared.

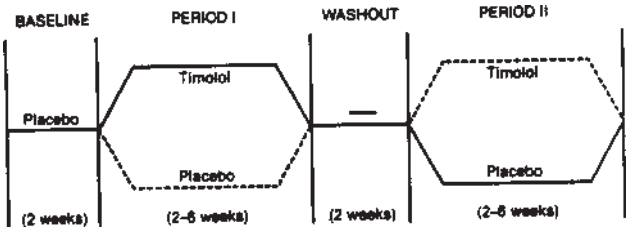


Fig. 1—Protocol design.

Dosage regimen—At the start of the initial treatment period, the patients were given on 10 mg tablet of timolol maleate b.i.d. or matching placebo. If after at least 3 days the number of VPDs had not been reduced by 70%, the dose was increased to a maximum of 30 mg b.i.d. of timolol or the same number of placebo tablets. Patients continued on their optimal dose to the completion of the treatment period.

Statistical methods—All data are presented as mean + SEM. The analyses of treatment differences shown by Holter parameters, vital signs, and laboratory safety parameters were based on Koch's nonparametric approach to the analysis of a two-period crossover designs. The results were corroborated by the same analysis on the ranks of the sums and differences of Periods I and II observations. Using a paired t-test the analyses were done on resting and exercise heart rates and on patients who had an adverse experience on one therapeutic regimen, but not the other. Before combining results from both, the data from each center were evaluated to determine if there were any significant differences. No significant differences were observed. Chi square analysis was used to compare the incidence of ventricular tachycardia during placebo and timolol treatment.

RESULTS

Twenty-eight of the 31 patients completed entire study. All parameters evaluated (age, sex, secondary diagnosis, prior therapy, concomitant therapy, and results of laboratory tests) were similar for both sequence groups (placebo-timolol and timolol-placebo) at baseline. The majority of the patients (64%, 18/28) required the maximum dose (30 mg b.i.d.), 11% (3/28) received 20 mg b.i.d., and 25% (7/28) received 10 mg b.i.d. The primary assessment of drug efficacy was based on 24-hour Holter monitoring results. The achievement of beta-blockade was determined by the decrease in peak exercise heart rate.

Holter Monitoring Diurnal variation (fig. 2)—Substantial diurnal variation was noted in both the heart rate and the frequency of ventricular arrhythmias. As a result, the Holter analysis was done on a 24-hour basis and also for the daytime (7 a.m. to 9 p.m.) and nighttime (9 p.m. to 7 a.m.) periods. The baseline heart rate was 86 ± 2 bpm in daytime compared with 74 ± 2 bpm in nighttime (p<.OOl). The number of VPDs/1000 heartbeats was 102 ± 17 in daytime and 79 ± 19 in nighttime (p<.02).

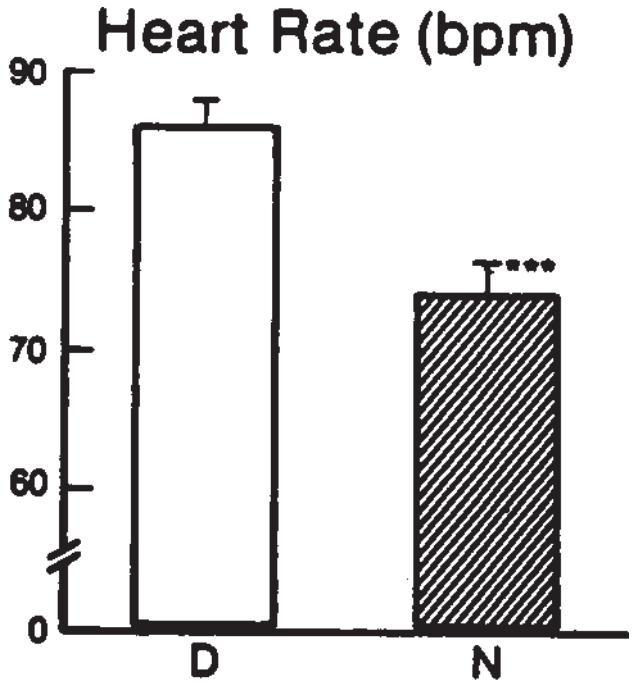
Efficacy analysis

Ventricular premature depolarizations (fig. 3)—There were 383 ±80 VPDs/24hr during the baseline period which increased to 414± 77 (p <.05) during the placebo, and decreased to 232 ±63 (p<.05) with the administration of timolol. The number of VPDs/1000 heart beats between 7 a.m. and 9 p.m. was 103±16 while patients received placebo, versus 67 ± 17 while they received timolol (p<.05). Between 9 p.m. and 7 a.m., the number of VPDs/1000 heart beats was 86 ± 15 with placebo and 67± 19 with timolol (p<.10). During the daytime hours, patients had significantly fewer hours at risk while taking timolol (67% ±4 than they did while taking placebo 85%± 1.5, p<.Ol).

Couplets (fig. 3)—The incidence of couplets also exhibited a diurnal variation. At baseline, the number of couplets/hours was 13 ±4 during daytime and 5 ±2.3 (p<.02) during nighttime. The administration of timolot reduced the number of couplets/24 hr from 239 ±84 at baseline to 44±17 (p<.05), while no significant change occured during placebo administration (214±3).

Ventricular tachycardia events (fig. 4)—Significantly fewer episodes of ventricular tachycardia (defined as three or more VPDs with a rate above 120/min) occured while patients were receiving timolol. This difference was statiscally significant (p<.001) both during the daytime and over 24 hours. During baseline, 46% of the patients had more than one VT event. This remained unchanged during placebo (31% NS), but declined significantly to 8% (p<.Ol) during timolol administration.

Mean heart rate (fig. 4)—The mean heart rate during placebo administration was higher in daytime



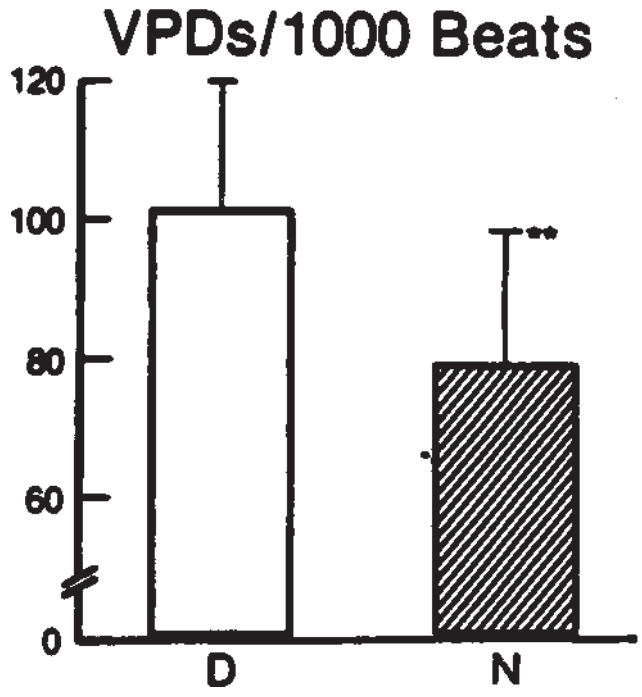


Fig. 2—Diurnal variation. D = daytime; N = nighttime, bpm = beats per minute, VPDs = ventricular premature depolarization ** = p <.01 *** = p<.001.

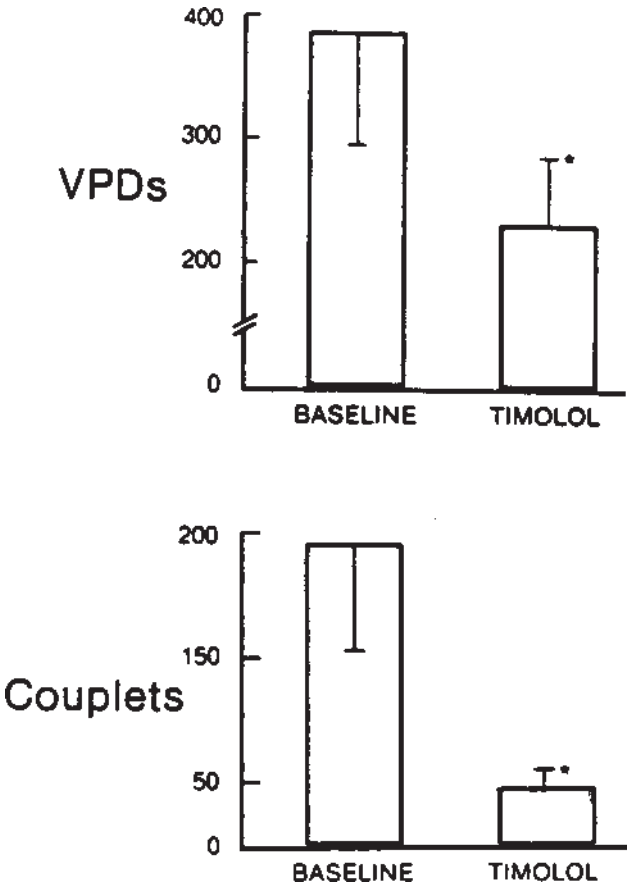


fig. 3—Effect of timolol in ventricular arrhythmias. VPDs = ventricular premature depolarization. * =p < .05 versus baseline.

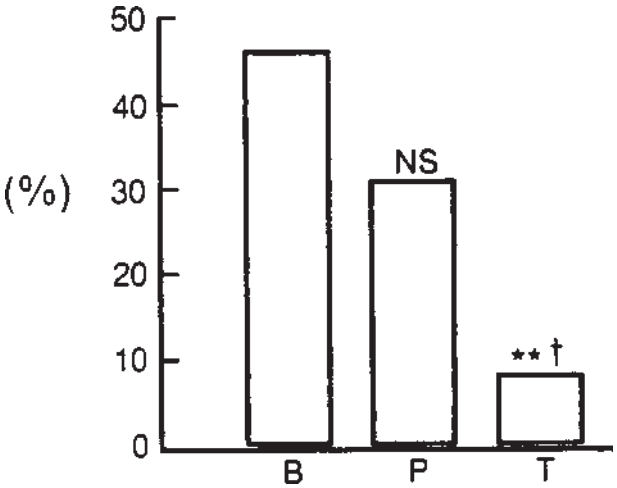


Fig. 4—Ventricular tachycardia incidence. B = baseline, P = placebo, T = timolol, NS = non significant. *. = p < .01 vs. baseline, T = p < .05 vs. placebo.

than nighttime during the baseline period. This difference was statistically significant: the daytime heart rate was 86 ±2 versus 71 ±1 beats/minute, (pc.001) Timolol maleate administration caused a reduction in mean heart rate to 62 ± 1 beats/minute during daytime (p<.001) but led to no further reduction during nighttime (60±2,p<.001).

Exercise testing—The mean duration of exercise was Similar for placebo (421 ± 16 seconds) and timolol (452 ±29 seconds). Fewer VPDs occurred during exercise in patients receiving timolol (14 VPDs/minute) than in patients receiving placebo (24 VPDs/minute). The difference did not reach statistical significance.

(p=0.10) This peak exercise heart rate was 150±4 beats/minute during placebo administration and 97 ±4 beats/minute (p<.01) when patients were receiving timolol. The most frequent reason for discontinuing exercise was fatigue. One patient stopped exercise due to ventricular tachyarrhythmia and another discontinued due to angina. Both patients were receiving placebo. Since the patients also had a significantly lower systolic and diastolic blood pressure while receiving timolol, there was a reduction in the double product (systolic blood pressure x heart rate) at the time of timolol administration.

Safety (Table 1)

Nineteen patients had at least one adverse experience during the study, including eight that were regarded as severe. Eleven patients reported side effects on both timolol and placebo; seven on timolol and one on placebo. The only patient who withdrew from the study due to an adverse experience was taking placebo at the time. The most common clinical adverse experiences in both groups were fatigue, headache and dyspnea. No laboratory values were considered adverse or serious. Timolol administration did lead to increases in the serum potassium, uric acid, and blood urea nitrogen levels, but these increases did not reach statistical significance.

TABELA I—Adverse experiences (Number of Patients).

	Placebo	Timolol
Fatigue	2	12
Dyspnea	2	5
Chest pain	0	4
Dizziness	1	2
Headache	3	2
Sweating	0	2
Trouble sleeping	1	2
Blurred vision	1	2
Loose stools	0	2
Nausea	0	2
Twitching eyes	0	2
Constipation	2	0

DISCUSSION

The prognostic significance of ventricular arrhythmias, including single VPDs, relevant to sudden death has been documented in many studies in pa tients with cardiac diseased [2,4,12]. Various beta-blockers have been studied and found to be efficacious in suppressing VPDs[13-16]. In fact, many beta-blockers have been shown to cause a 75% or greater suppression in the incidence of ventricular ectopic beats, a result that compares very favorably with that of such antiarrhythmics as quinidine and procainamide[12]. Furthermore, treatment with certain beta-blockers apparenfly reduces the death rate in post-myocardial infarction patients[8-10]. It is interesting to note, however, that while some beta-blockers can be dramatically efficacious in controlling malignant ventricular arrhythmias, others have very little impact on post-infarction mortality. Such an agent is sotalol, a non-cardioselective beta-blocker with both class II and III anti-arrhythmic activity[17] It has been shown that sotalol causes a reduction of up to 89% in the frequency of ectopic beats in patients who have suffered myocardial infarction[18]. However, a substantial multicenter placebo-controlled study was unable to demonstrate that sotalol reduces mortality in patients following an acute myocardial infarction[19].

Clinical studies have also led to some question about using certain beta-blockers in specific subgroups of patients. The Danish alprenolol study showed that the drug reduced the death rate among patients under, but not over, the age of 65 years[20]. A similar difference in the response of older and younger patients has been noted in the case of oxprenolol[21]. Another study showed no overall difference between the mortality rate of patients who received either oxprenolol or placebo after a myocardial infarction. In this study, patients who started beta-blocker treatment within five months of their myocardial infarction had a lower mortality rate than patients on placebo; however, the situation was reversed when patients started treatment more than a year after a myocardial infarction[22].

Although it is clear that the majority of beta-blockers are beneficial in patients following a myocardial infarction, the mechanism involved is not at all clear. The cardioprotective effects could be due to either anti-ischemic or antiarrhythmic effects or even both. Beta-blockade, by slowing the heart rate and altering the timing of events in the cardiac cycle, may also contribute to improve perfusion of blood-deprived areas of the heart muscle in post-infarction patients and protect the ischemic myocardium[23]. Several studies have provided evidence that beta blockers also increase the ventricular fibrillation threshold of the heart[24]. Although this property does not seem to be shared by all beta-blockers[25]. In addition, beta-blockade affects various metabolic processes in myocardial cells, including generation and utilization of free fatty acids[23]. There are also suggestions that beta blockers may be preferable to antiarrhythmic agents and should in fact be the drugs of choice for chronic treatment of ventricular arrhythmias[26], particularly because of their relatively mild side effects.

Beta-blockade may also have another advantage over classical anti-arrhythmic agents in the troublesome area of arrhythmia aggravation. Many antiarrhythmic drugs, as clinicians are coming to realize, can also have arrhythmogenic effects. These effects are more common than generally suspected. According to Hirsowitz, a review of single drug trials in 1,024 patients who had received 13 different agents showed that 11% experienced some “aggravation of ventricular arrhythimia”[27].

The choice of beta-blocker remains a problem, however beta-blocker differ from each other in chemi-

calstructure as well as electrophysiological and pharmacological properties. Efforts to link any of these properties with a beneficial effect have so far been unsuccessful [16,28], Some drugs that reduce mortality in pos~infarction patients are extremely lipophilic (propranolol) while others are moderatly lipophilic (metoprolol) or could be classified as hydrophilic (timolol). Some have active metabolites (propranolol) and others (timolol) do not. The list of drugs that clearly reduce post-infarction mortality includes both cardioselective (acebutolol, atenolol, metoprolol) and noncardioselective agents (nadolol, propranolol, timolol). Sympathomimetic activity is not the key either: timolol, propranolol, sotalol and metoprolol all lack intrinsic sympathomimetic activity. Propranolol and metoprolol, which prevent post-infarction mortality, and oxprenolol, which apparently does not, all have quinidine-like "local anesthetic" or membrane-stabilizing effects on the cardiac action potential (demonstrated by high dose animal studies). This property could, in theory, be associated with antiarrhythmic potency.

Our results in this study are similar to studies involving other beta-blockers [29-31] as well as other clinical trials of timolol [32,33]. We found that oral timolol therapy had a significant effect on heart rate, VPDs, couplets and VT events. The average 24 hour incidence of VPDs was reduced by 43% and that of couplets by 79%. Reduction of the incidence of VT was the most dramatic (96%). Ten of 12 patients in this study experienced more than one episode of VT in the 24 hours during the baseline period, compared with only one patient in the timolol treatment period.

It was interesting to verify the substantial diurnal variation in both heart rate and ventricular arrhythmias. The incidence of arrhythmias was much greater during daytime. Separate analysis of daytime and nighttime data thus improves the chances of detecting beneficial effects of antiarrhythmic drugs. We found that the antiarrhythmic effects of timolol are much more evident during daytime, probably due to the higher incidence of arrhythmia's during this period.

The findings that timolol causes no further decrease in heart rate during the night are of considerable interest. So is the lack of any suggestion of arrhythmogenic effects with this drug. It is also noteworthy that none of the patients who withdrew from the study did so because of the side effects of timolol.

These data allow us to conclude that oral timolol therapy is well tolerated and appears to be beneficial in reducing the frequency of VPDs, couplets and VT events in this patient population. This may explain, at least in part, how beta-blockers reduce the death rate in patients following an acute myocardial infarction.

RESUMO

O objetivo desse estudo foi avaliar as efeitos anti-arrítmicos do maleato de timolol, em portadores de extra-sístoles ventriculares prematuras freqüentes e multifocais (DVP), surto bigeminado e episódio de taquicardia ventricular (TV). Foi administrado maleato de timolol nas doses de 10 a 30 mg duas vezes ao dia a 31 pacientes, em estudo multiclínico duplo-cego, cruzado e controlado per placebo. A avaliação do grau de controle das arritmias ventriculares utilizou o eletrocardiograma dinâmico de 24 horas enquanto que o grau do beta-bloqueio foi determinado pela redução da freqüência cardiaca máxima em exercício. A administração do maleato de timolol causou decréscimo de: 36% na freqüência cardíaca em exercício, 39% no DVP/24 horas (de 383±80 a 232±63, p.<.05), 81% nos surtos bigeminados (de 239±84 a 44±17, p <0,05) e 83% na incidência de mais de um episódio de taquicardia ventricular (TV) durante as 24 horas de monitorização (de 46% a 8%, p< 0,01). Portanto o maleato de timolol, administrado em doses que produzam beta-bloqueio, é um agente promissor para o tratamento das DVPfreqüentes e multifocais, surtos bigeminados e episódios eventuais de taquicardia ventricular.

ACKNOWLEDGEMENTS

We would like to acknowledge Drs. P. E. Pool, A. F. Salel, Marlin and their clinical research stafifor the care and completeness in which this multicenter study was conducted. We would also like to thank Mr. Jaun Kagilaski and Sharon L. Kasdin, M. D. for their editorial assistance.

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