BENEFICIAL EFFECTS OF TIMOLOL IN DIGITALIZED PATIENTS WITH ATRIAL FIBRILLATION AND A RAPID VENTRICULAR RESPONSE

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Excessive exercise-induced tachycardia cannot be totally abolished by digitalis in patients with cronic atrial fibrillation (CAF). Therefore, 42 digitalized, CAF patients entered a study of oral timolol, a non-selective beta-blocker to determine the drug effect on ventricular response rate. The efficacy of reducing the ventricular response rate was confirmed by 24 hr Holter monitoring and exercise tolerance testing. In this ten-week, randomized. placebo-controlled, crossover, double-blind trial, timolol produced a 31% reduction in mean exercise heart rate (from 164.± 5.0 to 113±4.4 bpm, p < .01) and a decrease in mean arterial exercise blood pressure (from 88±1.5 to 81±1.9 mmHg, p<.01). Double product decreased from 27,396±1080 to 16,080±786, (p < .01). Furthermore, the daily Holter monitor mean heart rate was also decreased from 90±2.6 to 69±:2.0 bpm, p < .01). Seven timolol and one placebo patients were discontinued from the study because of adverse experiences; the most common symptoms were fatigue, dizziness, and dyspnea. Following an open label titration period, the dosage regimen of oral timolol was 10 mg b.i.d. in 82% of these patients.

In conclusion, oral timolol is efficacious and sale for most patients with chronic atrial fibrillation and concomitant use of digitalis.

Supraventricular arrhythmias are usually no life threatening but can be an important limiting factor in patients with coronary artery disease and impaired left ventricular function. Atrial fibrillation is a frequently encountered arrhythmia in patients with atherosclerotic heart disease, rheumatic mitral valvular disease and hypertensive heart disease. Since digitalis alone may not provide effective control of the rapid ventricular response in some patients with chronic atrial fibrillation [1-5], other agents, particularly beta-blockers [6,7] and calcium antagonists[8], are often added to the therapeutic regimen. The purpose of this study was to evaluate the efficacy and safety of an optimal dosage of oral timolol maleate, a non-selective beta blocker, in controlling rapid ventricular response in digitalized patients with chronic atrial fibrillation.

PATIENTS AND METHODS

This a multicenter study in which the patient pulation consisted of 42 patients, 38 males and 4 females etween the ages of 36 and 74 (mean age 93,6 ± 6.8 years) All patients had a primary diagnosis of chronic atrial fibrillation associated with a rapid ventricular response while receiving digitalis. These patients had a resting heart rate greater than 52 beats/minute; with exercise their heart rate increased to 120 or greater beats/minute or a minimum of 30 beats/minute from rest.

At the start of the one-week baseline period, patients had all previous beta-blocker therapy stopped. Digitalis was continued at the appropriate dose using digoxin tablets. Serum levels of digoxin, obtained in the morning prior to the next dose, were not to exceed 2.4 ng/ml by radioimmune assay. After removing beta blockers for at least three days, a complete physical examination, laboratory screening, an electrocardiogram, and a chest x-ray were performed. In addition, a 24 hour Holter cardiac recording and an exercise test using the Naughton exercise tolerance protocol were completed.

Baseline was followed by a three week open-label titration period with timolol. The patients initially received 10 mg b.i.d of timolol maleate in addition to digitalis therapy. At weekly intervals, the dosage of timolol was increased first to 20 mg b.i.d and then to a maximum of 30 mg b.i.d The upward ti-

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TABELA I - Parameter Evaluation Shedule.

	Baseline	Titration Period			Treatment I (Double-Blind		Treatment II (Double-Blind.	
Weeks	1	2	3	4	5	6	7	8
Drug	Washout	Timolol			Timolol † placebo Optimal		Placebo timolol Optiaml	
Dosage (b.i.d.)		10 mg	20 mg	30mg				
Holter	X	X	X	X	X		X	
EST	X	X	X	X	X		X	
ECG	X	X	X	X	X		X	

(†) Crossover at the end of Week 6. EST = exercise stress testing.

tration of timolol stopped if the patient had a 20% or greater reduction in heart rate at peak exercise testing when compared to baseline. The patients continued on the optimal dose of timolol to the end of the titration period. At weekly intervals in the titration schedule, an exercise tolerance test and 24hour continuous cardiac monitoring were performed.

Patients with a 20% or greater reduction in heart rate at peak exercise testing during the titration period compared to the baseline, entered the two-week treatment period I. Patients were randomly allocated to therapy with timolol or matching placebo. Those patients on timolol were maintained at the optimal dose established during titration. The digoxin dose was unchanged. At the end of this period, a complete physical examination, laboratory screening, an electrocardiogram, a 24 hour Holter recording and an exercise test were done.

In the two-week treatment period II, patients who received timolol during treatment period I received placebo, and those who received placebo now received timolol. Those patients on timolol were maintained at the optimal dose established during titration. The digoxin dose continued unchanged. At the end of this period, a complete physical examination, laboratory screening, an electrocardiogram, a Holter 24 hour cardiac recording and an exercise test were repeated (table I).

Statistical Methods - Conventional techniques were used to calculate means and standard deviations. Mean heart rate, resting and end-of-exercise parameters, duration, blood pressure, pulse and laboratory safety data were analyzed using a two-period crossover design. Nonparametric methods for a two-period crossover design were extended to account, for investigator differences. Investigator, treatment sequence, treatment and period main effects, and two-way interactions between investigator and the other main effects were evaluated through analysis variance on the ranks of the sums and differences of the period 1 and 2 observations[9].

The analysis of the efficacy parameter which changed from baseline to the end-of-titration and the end-of-titration to treatment, were performed by combining the Wilcoxon signed rank statistics for each investigator [10].

RESULTS

Efficacy - The administration of timolol maleate during the titration period caused a reduction in mean heart rate, determined by 24 hour Holter, monitoring, from the baseline period (90 ± 5 to 69 ± 4 beats/min, $p < 0.01$). At the end of titration the patients were randomized into either the Placebo or timolol group. There was no difference in the mean heart rate between these two groups (70 ± 4 vs 72 ± 5 bpm, ns) at the time of randomization.

In the placebo group, mean heart rate returned to 88 ± 2 bpm. by the end of two weeks. In the group receiving timolol, heart rate was 66 ± 2 bpm ($p < 01$) during the same period. At the end of period I , the patients were crossed over to the other treatment. The mean heart rate of the group receiving timolol during this second period decreased from go t 5 73 ± 8 bpm, $p < .05$; the mean heart rate of group receiving placebo increased from 65 ± 8 to 85 ± 7, $p < .05$. Figure I depicts the sequence7 table II summarizes the results.

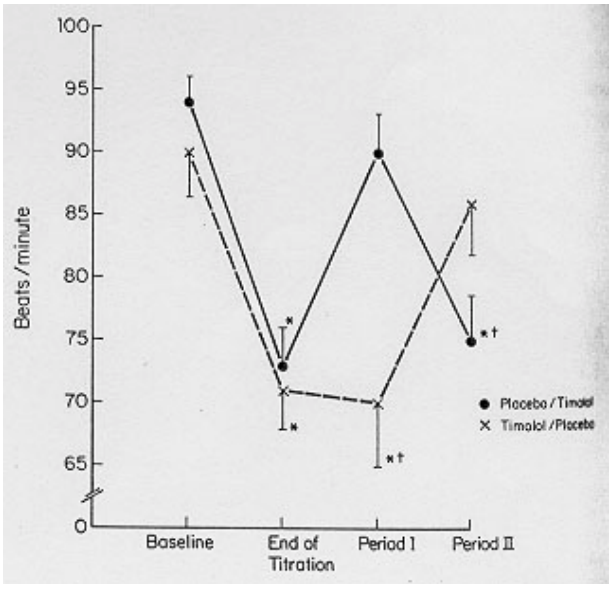

Fig.1 - Mean exercise heart rate before treatment, at the end of tiration, and at tne end of treatment periods I and II.(*=p < 0,05 vs baseline, + =p <0,05 vs placebol).

Both systolic and diastolic blood pressures were reduced by the administration of timolol during the titration period. This reduction was maintained during the double-blind period (table III).

TABELA II - Resting Mean Heart Rate.

	N	Baseline	End of Titration	N	Timolol	Placebo
Mean Heart Rate (beats/min)	34	90 ± 15.5	69 ΔΔ ± 11.8	31	71** ± 17.5	87 ++ ± 19.3

ΔΔ Significantly different from baseline, p <.01; ++ Significantly different from end of titration, p < .01; ** Siginificantly different from placebo, p < .01.

TABELA III - Sitting Arterial Bllod Pressure

Blood Pressure	Baseline	End of Titration	Timolol	Placebo
Systolic	135 ± 13	125 ± 14 ΔΔ	126 ± 16*	135 ± 17 ΦΦ
Diastolic	84 ± 8	76 ± 7 ΔΔ	76 ± 10**	83 ± 9 ΦΦ

ΔΔ Significantly different from baseline, p < .01; *, ** Significantly different from placebo, p < .05, p < .01, respectively; ΦΦ Significantly different from end of titration, p < .01. The values represent pooled data from the end of both treatment periods.

Exercise Tolerance Test - Exercise duration, heart rate, blood pressure and double product (heart rate x systolic blood pressure) were evaluated and compared at baseline, end of titration and during the two treatment periods.

Timolol administration reduced all the above parameters with the exception of exercise duration.(table IV). At the end of titration, only two patients failed to achieve a 20% reduction in maximal exercise heart rate; they had a 15 and 17% reduction, respectively. During treatment with placebo, patients had a significant increase in all parameters from the end of titration.

TABELA IV - Exercise Stress Test.

	Baseline	End of Titration	Timolol	Placebo
Systolic BP	174 ± 23	142 ± 24 ΔΔ	151 ± 24**	170 ± 29 ΦΦ
Diastolic BP	88 ± 8	81 ± 11 ΔΔ	83 ± 11	87 ± 12 Φ
Heart rate	164 ± 29	113 ± 23 ΔΔ	114 ± 28**	159 ± 32 ΦΦ
Double Product	27,396 ± 6,263	16,084 ± 4,559	17,350 ± 5,111	26,736 ± 6,588
Duration(sec)	731	781	824	866 Φ

ΔΔ Significantly different from baseline, p < .01, ** Significantly different from placebo. p < .01;Φ, ΦΦ Significantly different from end of titration, p < .05, p < .01 respectively; 1 Patients received either timolol or placebo in a randomized crossover design following titration. The values represent pooled data from the end of both treatment periods.

Safety - Nine patients receiving placebo and 20 Patients receiving timolol (titration and/or treatment period) had one or more adverse experiences. Eight patients withdrew from the study due to clinical adverse experiences, seven on timolol and one on placebo. All seven timolol patients withdrew during the titration period. Only 1 titration patient had an adverse experience which was considered serious by investigator (dizziness, dyspnea and bronchial spasm). One placebo patient withdrew from the study on day 4 of treatment period II due to anxiety, vasodilation, and paresthesia. This was not considered by the investigator. The most common adverse experiences with placebo were fatigue/ tiredness, nervousness, and headache. The most common adverse experiences of patients on timolol were /tiredness, dizziness, and dyspnea. One patient on placebo had nine laboratory parameters outside the normal range and considered adverse by the investigator. Three patients on timolol had one parameter outside the normal range and considered adverse by the investigator. None of these laboratory parameter values were considered seriously abnormal.

DISCUSSION

It has been clearly demonstrated that betablockers are beneficial in patients following an acute myocardial infarction [11-13]. The mechanisms by which timolol, propranolol and metoprolol reduce cardiac mortality were not the goal of these studies. However, the hypothesis is that the beneficial action is due to a combination of both anti-ischemic and anti-arrhythmic properties. Beta-blockers have been shown to be efficacious antiarrhythmics in patients with malignant ventricular arrhythmias [14-16]. Beta-blockers are also useful in the treatment and prevention of supra-ventricular arrhythmias [17], including atrial-fibrillation [6,7]

Atrial fibrillation is a frequently encountered arrhythmia in patients with diseases such as atherosclerotic heart disease, rheumatic mitral valvular disease and hypertensive heart disease. The therapeutic goal in the treatment of chronic atrial fibrillation is the control of the rapid ventricular rate both at rest and during exercise [18]. In some patients, digitalis alone may not be effective in controlling the rapid ventricular response [1-5]. Therefore, additional agents are often added to the therapeutic regimen [6-9].

Both calcium antagonists, especially verapamil [8,9], and beta-blockers [6,7] prolong the refractory period in the A-V node and consequently can be useful in decreasing the ventricular response in patients with atrial fibrillation.

In this study, timolol maleate was evaluated in patients with chronic atrial fibrillation who were receiving digitalis. All eligible patients initially received timolol maleate 10 mg b.i.d. orally in addition to digoxin therapy. The dosage of timolol was titrated upward at weekly intervals but not exceeding the maximum dose of 30 mg b.i.d.

Eighty-two percent of the patients studied were maintained on a dosage of timolol of 10 mg b.i.d. Timolol in this dosage caused a substantial reduction in the ventricular response both at rest and during exercise. Other cardiovascular parameters, such as blood pressure (systolic, diastolic and mean arterial) and double product, were also reduced. These beneficial results were accomplished without altering the exercise duration.

The reduction of mean heart rate with timolol is consistent with studies in the literature by Ferguson et al [19] in normal volunteers and David, et al [5], in patients with chronic atrial fibrillation. In addition, David, et al [5], showed that timolol treatment was effective In reducing both exercise an resting heart rate beyond the effects of digoxin (particularly exercise heart rate) in patients with chronic atrial fibrillation. Furthermore, timolol was shown to be efficacious in reducing the ventricular response rate in patients with chronic atrial fibrillation even

without titration to the degree of reduction in exercise heart rate[20].

Double product is an index of myocardial oxygen consumption which is greatly increased, during exercise and is proportional to the intensity of exercise [21]. A reduction in double product (myocardial oxygen consumption) is very important in patients with chronic atrial fibrillation and underlying coronary artery disease. Furthermore, it has been shown that patients with stable angina pectoris experience onset of pain at a particular heart rate and blood pressure[22] The reduction in double product seen in this study confirms the findings of Vukovich in normal volunteers [23] in which timolol decreased both systolic blood pressure and heart rate during exercise.

The side effect profile with timolol was low and discontinuation of therapy due to clinical adverse experiences occurred in 8 patients .(7 patients on timolol, one on placebo). Only one patient on timolol had an adverse experience considered serious by the investigator (dizziness, dyspnea, and bronchial spasm). The most common clinical adverse experiences reported with timolol were fatigue/tiredness, dizziness and dyspnea.

This study's results confirm the data in the literature showing that beta-blockers, including timolol, are effective in lowering resting/exercise ventricular response rate and double product in patients with chronic atrial fibrillation. This response is attained at doses of timolol that are well tolerated in patients with chronic atrial fibrillation who are also receiving digitalis.

RESUMO

Quarenta e dois pacientes com fibrilação atrial crônica e em uso de digitálico foram tratados com timolol.

A redução da freqüência ventricular foi avaliada através do teste de esforço e de monitorização contínua pelo sistema Holter O estudo teve duração de 10 semanas e foi duplamente cego, aleatório, com Um grupo placebo e um grupo tratado com timolol.

A administração de timolol, na dose média de 10 mg, duas vezes por dia, produziu uma diminuição de 31 % na freqüência cardíaca (de 164 ± 5 para 113 ± 4 bpm, p < 0,01) e na pressão arterial média (de 88 ± 1,5 para 81 ± 1,9 mmHg) durante o teste na esteira rolante.

O duplo-produto reduziu-se de,27,396 ± 1080 para 16,080 ± 786 (P < 0,01).

A freqüência cardíaca determinada diminuiu de 90 ± 3 para 69 ± 2 bpm (p < 0,01).

Sete pacientes tratados com timolol e um paciente tratado com placebo foram retirados do estudo em virtude dos efeitos colaterais (fadiga, tonteira e dispnéia).

Conclui-se que a administração de timolol é eficaz e segura em pacientes com fibrilação atrial crônica e uso concomitante de digitálico.

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