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Talinolol in Patients with Stable Angina Pectoris and Concomitant Hypertension

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This open, post marketing surveillance study evaluates the efficacy and tolerability of talinolol, a cardioselective beta-blocker with no intrinsic sympathomimetic activity, in the treatment of patients with stable angina pectoris and concomitant hypertension. Following a 7-day washout period, 25 adult patients received 100 mg talinolol once daily in the morning for 20 days as inpatients, and subsequently for three months on an outpatient basis. Clinical and haemodynamic parameters were assessed at baseline, after 24 hours, at the end of the inpatient stage at day 20, and following a further 70 days of outpatient treatment. The incidence of anginal attacks decreased from 4.2 ± 0.5 per week at baseline to 0.9 ± 0.3 per week after 20 days ($p < 0.05$) and to 0.6 ± 0.2 per week ($p < 0.05$) at the end of the total 90 days' treatment. Parallel, reductions were seen in weekly nitroglycerine consumption. Adequate blood pressure control was achieved after 24 hours of treatment and was maintained over the entire treatment period. Compared to baseline values, systolic blood pressure decreased by 12.1 % after 24 hours and by 13.3 % at study endpoint ($p < 0.05$). Diastolic blood pressure values were reduced by 7.1 % ($p < 0.05$) and 14.3 % ($p < 0.05$) respectively. Other efficacy parameters (ie, heart rate, ECG monitoring, ergometric tests) showed further positive treatment effects. Talinolol was well tolerated, with no evidence of significant adverse events. An overall improvement in general health-related symptoms (headache, dizziness, sleep disorders etc.) was noted at the end of treatment. Talinolol at a dose of 100 mg once daily is thus an effective and well tolerated anti-anginal and anti-hypertensive agent in patients with ischaemic heart disease and concomitant hypertension. *J Clin Basic Cardiol 2000; 3: 129–31.*

Key words: talinolol, cardioselective beta-blocker, angina pectoris, hypertension

Beta-adrenoreceptor blocking agents (beta-blockers) competitively inhibit the action of catecholamines at beta-adrenergic receptor sites. These agents have been extensively and successfully used in the treatment of a range of cardiovascular disorders [1, 2]. They can be classified according to their differential affinities for $beta_1$ receptors, which are found mainly in the heart, and $beta_2$ receptors, found mainly in bronchial tissue. Unlike the earliest beta-blockers, which were nonselective, cardioselective beta-blockers have a greater affinity for $beta_1$ receptors, although the selectivity is not absolute. The cardioselective beta-blockers include well-known agents such as atenolol and metoprolol.

Talinolol (Cordanum® 100) belongs to the group of cardioselective $beta_1$ blockers lacking intrinsic sympathomimetic activity. The selectivity of talinolol to $beta_1$-adrenoreceptors is markedly greater than that of atenolol and is comparable to the selectivity of metoprolol [3]. In therapeutic doses (50–300 mg/day) talinol therefore has no nonspecific blocking effect on $beta_2$-adrenoreceptors. Talinolol has been used in the treatment of cardiovascular disorders, notably mild to moderate hypertension but also ischaemic heart disease, acute myocardial infarction and cardiac arrhythmias, for over two decades [4, 5]. As with other beta-blockers, it is also increasingly used to treat heart failure [6, 7]. Talinolol has a long plasma half-life (11.9 ± 2.4 hours) [8], which ensures the therapeutic effectiveness of a once-daily 100 mg dosage over the whole 24 hours. This is an advantage from the point of view of patient compliance, which improves as the frequency of dosing decreases, and also pharmacokinetics, as once-daily dosing provides a more constant daily plasma level of active substance. Furthermore, talinolol has been shown to have no detectable negative effects on glucose metabolism or lipid parameters [9, 10].

The purpose of this open post marketing surveillance study was to evaluate the clinical and haemodynamic effects of talinolol treatment on blood pressure, central and internal cardiac haemodynamics, cardiac arrhythmias, tolerance of physical exercise, and lipid metabolism, as well as its overall tolerability, in patients suffering from ischaemic heart disease with concomitant hypertension.

Materials and Methods

In total, 25 patients were enrolled in the trial (male = 12, female = 13). The principle criteria for inclusion of patients into the trial were hypertension stage II (sitting diastolic blood pressure 100–109 mmHg and sitting systolic blood pressure 160–179 mmHg), and concomitant ischaemic heart disease (exercise-induced angina, functional classes II–III). The mean age of patients was 60.3 ± 1.8 years with a range of 45 to 75 years. Mean body weight was 71 ± 7 kg, range 57.0–90.0 kg. Five patients had a previous history of myocardial infarction. Twenty patients were currently receiving concomitant medication for their condition: nitroglycerine, mean dosage 2.9 ± 0.4 mg/day: 14 patients; hydrochlorothiazide, mean dosage 2 × 25 mg per day: 6 patients. For the patients with ischaemic heart disease the mean duration of illness was 12.2 ± 3.6 years, while for patients with essential hypertension it was 19.7 ± 6.1 years. Written informed consent was received from all patients before the start of any trial procedures. All current anti-hypertensive and vasoactive drugs, cardiac glycosides and diuretics, with the exception of nitroglycerine and hydrochlorothiazide, were discontinued on entry into the 7-day wash-out period.

At the end of this period, the patients' baseline characteristics, including clinical and haemodynamic parameters, were evaluated. Patients were then given 100 mg talinolol

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once daily in the morning for 20 days in hospital, and thereafter for a further 70 days on an outpatient basis. Clinical and haemodynamic parameters were reassessed after 24 hours, at the end of inpatient treatment on day 20, and at the end of treatment (90 days). Efficacy variables included the change from baseline to endpoint evaluation in the frequency of anginal attacks, requirement for rescue nitroglyceride, arterial blood pressure (BP) and heart rate. The parameters of central and internal cardiac haemodynamics (heart rate index, cardiac output, ejection fraction and left ventricular mass, LVM) were all determined using a Fukuda (Japan) echocardiograph. Blood pressure was measured and ECG monitored daily using the Schiller MT-7 (Switzerland) system. Anti-anginal effect was assessed by a decreased number of ischaemic episodes (depression of the ST segment under the isoelectric line of 1 mm for more than 60 seconds). A further indication was the decreased frequency of sinus tachycardia (increase in heart rate above 130 bpm). Ergometric tests were also performed using physical exercise of known duration and intensity according to a modified Naughton protocol on a bicycle ergometer [11, 12], and measuring the frequency of cardiac arrhythmias at exercise peak.

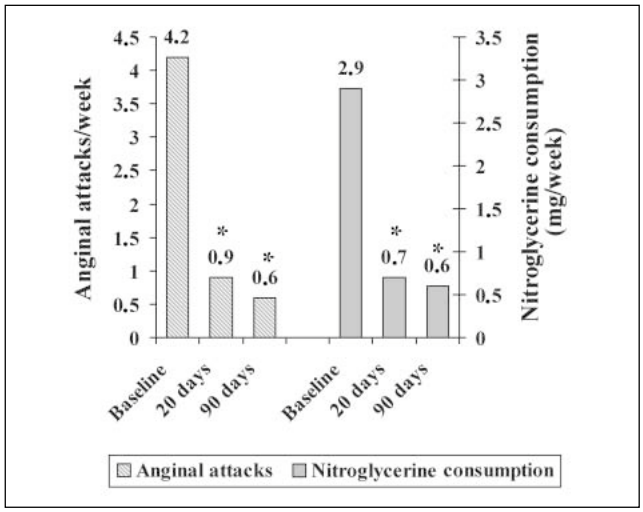

Figure 1. Change in number of anginal attacks and nitroglycerine consumption during treatment (*p < 0.05 vs baseline value)

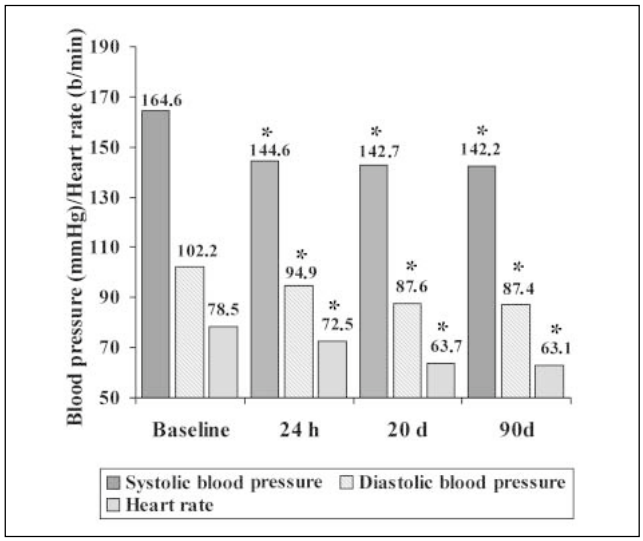

Figure 2. Change in mean systolic and diastolic blood pressure and in heart rate during treatment (*p < 0.05 vs baseline value)

The criterion for evaluating safety and tolerability was the change in frequency of general health-related symptoms at study endpoint compared to baseline. Laboratory parameters, including total cholesterol, triglycerides, and low- and high density lipoproteins, were assayed using Lab-System SP-901 TM, Finland.

The results were analysed using variation statistical methods including Student's t-test and comparing matched pairs, using the statistics program Statgraph. Values were regarded as statistically significant for $p < 0.05$.

Results

Efficacy

Following talinolol treatment, the number of anginal attacks decreased from a mean of 4.2 ± 0.5 per week at baseline to 0.9 ± 0.3 after 20 days ($p < 0.05$) and to 0.6 ± 0.2 at 90 days ($p < 0.05$) (Figure 1). In parallel, the mean amount of nitroglycerine used decreased from 2.9 ± 0.4 mg/week to 0.7 ± 0.3 mg/week at 20 days and to 0.6 ± 0.2 mg/week after 90 days ($p < 0.05$).

There was a 12.1 % reduction in systolic blood pressure from a mean 164.6 ± 4.3 mmHg to 144.6 ± 3.5 mmHg after 24 hours, a 13.3 % reduction to 142.7 ± 3.4 mmHg after 20 days, and a 15.8 % reduction to 142.2 ± 3.2 mmHg at the end of treatment after 90 days (Figure 2). The corresponding values for diastolic blood pressure were 7.1 % (102.2 ± 2.6 to 94.9 ± 2.4 mmHg), 14.3 % (87.6 ± 2.1 mmHg) and 14.5 % (87.4 ± 1.9 mmHg). After 24 hours of treatment, heart rate fell by 7.6 % ($p < 0.05$), by 18.8 % after 20 days and by 19.6 % after a total 90 days of treatment ($p < 0.05$) (Figure 2).

Daily ECG monitoring showed a 2.7-fold reduction from baseline to 90 days in the incidence of ventricular extrasytoles (from a mean 254 ± 49/h to 94 ± 18/h, Table 1), while the number of supraventricular extra systoles fell 10.5 times (from a mean 134 ± 20/h to 13 ± 5/h, $p < 0.05$). At baseline, 24-hour cardiomonitoring showed a mean of 38 events per day of sinus tachycardia, but none were observed on monitoring at 90 days. There was a mean of 28 ischaemic episodes (ST segment depression) per patient over 24 hours before talinolol treatment. This was reduced to a mean of 7 episodes over 24 hours after treatment, ie, a fourfold decrease (Table 1).

After the first 20 days of inpatient treatment, the bicycle ergometer test did not reveal any statistically significant changes in duration and peak load of exercise (Table 2). At the 90-day assessment, however, an increase in the

Table 1. Change in cardiac parameters during treatment

	Baseline	90 days
VES (mean/h)	254 ± 49	94 ± 18
SVES (mean/h)	134 ± 20	13 ± 5*
Sinus tachycardia (episodes/24 h)	38	0

*p < 0.05; VES, ventricular extra systoles; SVES, supraventricular extra systoles; Sinus tachycardia defined as episodes of heart rate greater than 130 bpm

Table 2. Effect of talinolol on the duration and intensity of bicycle ergonometer exercise

	Baseline	20 days	90 days
Mean duration (s)	415 ± 43	408 ± 27	570 ± 53*
Mean intensity (W)	81 ± 8	79 ± 7	108 ± 8*

*p < 0.05

duration of physical exercise of 37.3 % and in the peak load of the last stage of exercise of 33.3 % ($p < 0.05$) was detected.

Safety and tolerability

The safety and tolerability of talinolol were evaluated by the reporting of any change in health-related symptoms at assessments from baseline to the end of the trial. Headache, dizziness and muscular weakness were the most frequently reported symptoms assessed as disease-related before treatment (each reported by 19 patients, and these in fact decreased in frequency to 8, 10 and 4 patients respectively at 90 days (Table 3) as a consequence of talinolol therapy. Reports of anginal pain decreased from 17 at the start to 2 patients at the end of treatment, cardiac arrhythmias from 12 to 4 patients, flushing and sweating from 12 to 3 patients, and sleep disorders from 7 to 5 patients (Table 3). Overall, the subjective tolerability of talinolol therapy was evaluated as good. Only one patient reported an additional negative physical symptom (weakness and dizziness) which was considered to be related to the study drug. These side effects appeared as soon as the patient started to take 100 mg talinolol/day. After 1 week the symptoms persisted and therefore the dosage was reduced, and the symptoms resolved.

No cardiodepressive effect on the myocardium was observed; in fact there was an increase in ejection fraction from 54 ± 2 % at the baseline to 56 ± 2 % at the end of 90 days of talinolol treatment ($p < 0.05$). No significant changes in plasma lipids were observed with long-term talinolol treatment, in contrast to the commonly-observed effect of other beta-blockers [13].

Discussion

This study was designed to evaluate the response of patients with angina pectoris and hypertension to talinolol therapy, using a variety of clinical and cardiac haemodynamic parameters in addition to blood pressure reduction and overall tolerability. The results confirm talinolol's efficacy as an anti-hypertensive, producing significant reductions in diastolic and systolic blood pressure which were observable within 24 hours of the start of treatment. A single oral administration of 100 mg of the drug in the morning gave adequate blood pressure control over the first 24 hours. The effect was increased after 20 days and maintained over the entire 90-day period of active treatment, with no further significant increase between 20 days and 90 days. Talinolol's anti-anginal efficacy was demonstrated by the decline both in incidence of anginal attacks and in the use of nitroglycerine. A significant fall in heart rate was also observed in the course of the trial, indicative of more economical cardiac work and a reduced requirement for cardiac oxygen. Finally, after 90 days, marked and significant increases in the duration and intensity of physical exercise were noted. These exercise changes were not apparent at the earlier assessments after only 20 days of treatment. Thus, although talinolol's positive effects on blood pressure can be seen very soon after the start of treatment, there are additional clinical benefits associated with longer administration.

Additional clinical benefits associated with longer treatment concern the positive effect of talinolol on lipid profile in comparison to other beta-blockers [14].

The overall tolerability of talinolol was assessed as good. This was supported by the low level of reported adverse events, absence of additional health-related symptoms, and the fact that all 25 patients completed their inpatient treatment with talinolol and voluntarily continued treatment on an outpatient basis to the end of the study. Talinolol's long plasma half-life permits once-daily dosing. Long-acting formulations providing 24-hour efficacy are preferable to short-acting agents for a number of reasons [15]: the consequently smoother plasma profile of active substance is conducive to better tolerability and a lower incidence of side effects, patient compliance is improved, and protection is provided against the effects of the sudden increase in blood pressure in the early morning.

Since beta-blockers and diuretics have been shown to reduce cardiovascular morbidity and mortality in controlled clinical trials [16], they are the recommended first-line medications for the treatment of hypertension [15]. Other anti-hypertensive agents may be equally efficacious in reducing blood pressure, but reduction of long-term cardiovascular morbidity and mortality has not yet been proven. This study shows that when taken as a single 100 mg dose each morning, the cardioselective beta-blocker talinolol reduces and maintains the achieved blood pressure level, reduces the incidence of anginal attacks and the need for nitroglycerine, increases the functional reserves of the heart during exercise, and alleviates health-related symptoms.

Table 3. Effect of talinolol on reported health-related symptoms during treatment

Health-related symptom	Number of patients	
	Baseline	90 days
Headache	19	8
Dizziness	19	10
Muscular weakness	19	4
Anginal pain	17	2
Emotional reactions	17	15
Lethargy	15	9
Lack of concentration	13	4
Flushing, sweating	12	3
Cardiac arrhythmias	12	4
Restlessness	10	5
Fatigue after sleep	10	3
Irritability	9	6
Sleep disorders	7	5

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