Double-Blind Randomized Multicenter Study on the Efficacy of Trapidil versus Isosorbide Dinitrate in Stable Angina Pectoris

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Summary

Background: Trapidil is an inhibitor of phosphodiesterase I-IV with resulting positive lusitropic, vasodilating, and antiplatelet effects.

Hypothesis: This study was undertaken to compare the antianginal efficacy of trapidil with that of isosorbide dinitrate (ISDN) in patients with stable angina pectoris.

Methods: We studied 95 patients with stable angina pectoris who were randomized into a double-blind parallel group study with either oral trapidil or ISDN. After a 1-week run-in period and a 2-week wash-out phase, the patients received either trapidil 200 mg t.i.d. (n = 48) or ISDN 20 mg t.i.d. (n = 47) for 12 weeks. All antianginal medication, except sublingual glyceryl trinitrate (GTN), was discontinued during the study. Patients underwent an exercise electrocardiogram on an ergometer bicycle according to a modified Bruce protocol before and at 6 and 12 weeks during treatment.

Results: The workload capacity increased from 583 ± 281 W·min before treatment to 833 ± 444 W·min after 12 weeks of treatment in the trapidil group (p<0.01) and from 555 ± 276 W·min to 827 ± 361 W·min in the ISDN group (p<0.01). The anginal attacks per week as well as the use of GTN decreased significantly in both groups. After 12 weeks of therapy, the cumulative ST-segment depression during exercise decreased by 67% in the trapidil patients and by 23% in the ISDN patients. Compared with baseline, the double product at the 75 W level was reduced in both groups after 12 weeks of treatment. Blood pressure and heart rate at rest remained nearly unchanged. Overall, no statistical difference was found between the two study groups. The tolerability was good.

Conclusion: Oral trapidil therapy is safe and effective in stable angina pectoris and is equivalent to standard therapy with ISDN.

Key words: trapidil, isosorbide dinitrate, angina pectoris, workload capacity

Introduction

Trapidil, a triazolopyrimidine, is an unspecific inhibitor of the phosphodiesterase I-IV and structurally and pharmacologically not related to nitrates, calcium-channel blockers, or beta blockers.[1]

In clinical trials, trapidil exhibits a positive lusitropic effect that leads to reduced left ventricular end-diastolic pressure in patients with coronary heart disease.[2] The vasodilation induced by trapidil leads to a diminished cardiac preload and, to a lesser extent, to a diminished afterload with a subsequent decrease in myocardial oxygen consumption.[3]

An antiplatelet effect, based on an increased endothelial release of prostacycline and on an inhibited thromboxane A_2 synthesis, has been proven for trapidil.[4,5] The platelet-derived growth factor (PDGF) antagonism of trapidil has been demonstrated in animal studies[6] and lead to a significant reduction of restenosis after percutaneous transluminal coronary angioplasty (PTCA) in clinical trials.[7-9]

In patients with unstable angina pectoris, the additional administration of trapidil could reduce the incidence of infarction and mortality.[10] In stable angina pectoris, several clinical studies have proven the antianginal efficacy of trapidil,[4,11-13] but no study compared trapidil with an organic nitrate. In the present study, the antianginal efficacy of trapidil and isosorbide dinitrate (ISDN), an approved standard antianginal medication, was assessed in patients with stable angina pectoris.

Methods

Patients

In all, 99 patients with stable angina pectoris were included in the double-blind study and were randomized into two par-

allel groups, receiving either orally ISDN 20 mg t.i.d. (plain release) or trapidil 200 mg t.i.d. The patients took the medication every 6 h during the day, with a nitrate-free interval during the night.

Inclusion criteria were stable angina pectoris of class II or III according to the Canadian Cardiovascular Society classification, with a history of exertional chest pain, stable for at least 3 months prior to medication. Chronic ischemic heart disease was assessed by stenosis in previous coronary angiography, reproducible signs of ischemia in exercise electrocardiogram (ECG), and/or previous myocardial infarction (MI). Patients with unstable angina pectoris, cardiac failure New York Heart Association (NYHA) classification III or IV or previous MI, bypass surgery, or PTCA in the past 3 months were excluded from the study.

All patients gave written informed consent before entry. The study was approved by the local Ethics Committee, and conducted in accordance with the Declaration of Helsinki and audited by a Quality Assurance Unit.

Study Protocol

The study was designed as a randomized, double-blind, comparative trial with two parallel groups. After inclusion, a placebo run-in phase of 1 week and a wash-out phase of 2 weeks followed. During the wash-out phase, all previous antianginal medications except for glyceryl trinitrate (GTN) were withdrawn. The subsequent double-blind verum treatment phase lasted 12 weeks. Throughout the entire study period, except for 2 h before the exercise ECG, the patients had free access to GTN to treat their angina pectoris attacks. They had to note their angina pectoris attacks and their GTN use in a diary.

At baseline and after 6 and 12 weeks of treatment (1 h after the supervised drug intake), an exercise ECG was performed at the same time of the day on an ergometer bicycle according to a modified Bruce protocol. The exercise ECG was started at a workload of 50 W and was increased stepwise by 25 W every 3 min. A 12-lead ECG was made before and during the exercise ECG and was recorded every min. The following parameters were determined: (1) product of maximal workload and exercise time (i.e., workload capacity); (2) exercise duration; (3) ST-segment depression measured 80 ms beyond the J point (the mean value was calculated from five consecutive beats in the lead with the most pronounced ST-segment depression); (4) product of the mean arterial pressure and heart rate at 75 W (i.e., double product); (5) resting blood pressure and heart rate; (6) blood pressure and heart rate at maximal individual workload and 3, 6, and 10 min after exercise.

The exercise ECG was terminated according to the guidelines for cardiac exercise testing.[14]

Statistical Analysis

To estimate the sample size, a clinically relevant difference in the treatment success (d = 80 W·min), a difference between the groups of d/2 = 40 W·min at a maximum, a standard deviation (SD) of s = 75 W·min, and probabilities of α (one-tailed)

= 0.05 and β = 0.2 were assumed. With these values, a sample size of n = 44 patients per group was calculated for significant demonstration of the equivalence of both treatments.

Statistical significance was assessed using the two-sample Wilcoxon rank sum test and the nonparametric Mann-Whitney-U test for unpaired samples. A p-value of < 0.05 was assessed to be significant. Values are expressed as mean ± SD and in the figures as mean ± standard error of the mean (SEM). The primary efficacy variable, that is, the workload capacity, was evaluated by an intent-to-treat analysis. The secondary efficacy variables were evaluated by a per-protocol analysis (patients who did not finish the study were taken into account with their last available data, i.e., "last-value-carried-forward" procedure).

Results

Patient Characteristics

Fifty patients in 15 medical facilities were randomized to trapidil (Group 1) and 49 patients to ISDN (Group 2). Four patients (two in each group) had to be excluded from evaluation because they did not take the study medication. Patient demographics, cardiovascular disease history, and antianginal pretreatment are listed in Table I. The demographic data showed no significant difference between the two groups.

Exercise-induced angina pectoris was proven by ST-segment depression during exercise ECG in all patients. Twenty-

TABLE I Patient characteristics

	Trapidil (n = 48)	ISDN (n = 47)
Demographic data (mean ± SD)		
Age (years)	54 ± 9.5	56.7 ± 10.6
Gender (F/M)	10/38	14/33
Height (cm)	172 ± 8	168 ± 8
Weight (kg)	81.7 ± 12	76.5 ± 12.2
History of cardiovascular disease[a]		
Myocardial infarction	26	33
Coronary angiography	10	10
Bypass surgery	3	5
PTCA	4	4
Hypertension	23	21
Diabetes mellitus	8	4
Hyperlipidemia	25	26
Smokers	12	5
Antianginal pretreatment[a]		
Calcium-channel blockers	15	15
Beta blockers	15	16
Long-acting nitrates	7	9
Double therapy	9	10

[a] Multiple nominations are possible, details see text.

six Group 1 and 33 Group 2 patients had a previous MI. Except for patients with a previous MI, coronary artery disease was proven in 10 further patients (7 in Group 1, 3 in Group 2) by coronary angiography (with or without PTCA/bypass surgery), and in 6 further patients (4 in Group 1, 2 in Group 2) by thallium scintigraphy. Thallium scintigraphies showed transient perfusion defects on exercise. Therefore, beside ST-segment depression during exercise ECG, chronic ischemic heart disease was proven with one further parameter in 37 of 48 Group 1 patients and in 38 of 47 Group 2 patients. Echocardiography was recorded in 23 Group 1 and 27 Group 2 patients, detecting hypokinetic myocardial areas in 12 and 17 patients, respectively.

Exercise Electrocardiogram

Workload capacity was of the same order of magnitude in both groups upon initial and final exercise ECG (Table II). The workload capacity increased significantly from 583 ± 281 W·min before treatment to 883 ± 444 W·min after 12 weeks of treatment in Group 1 (p<0.01) and from 555 ± 276 W·min to 827 ± 361 W·min in Group 2 (p<0.01) (intent-to-treat analysis) (Fig. 1). The increase in the per-protocol analysis was also significant (Table II). According to the Mann-Whitney-U test, the two drugs are of equivalent efficacy with respect to the primary parameter of efficacy.

After 6 weeks of treatment the percentage of patients who showed an increase in workload capacity was 46% in Group 1 (22/48) and 51% in Group 2 (24/47) with a further increased response to 60 and 57% after 12 weeks of treatment (intent-to-treat analysis). Regarding the per-protocol analysis, the responder rate after 12 weeks was 78% in Group 1 and 68% in Group 2. Eight Group 1 patients showed no change or decrease in workload capacity compared with 13 patients in Group 2.

The maximum individual workload as well as the exercise duration also increased during therapy (Table II). While the

TABLE II Effect of oral trapidil (200 mg t.i.d.) and ISDN (20 mg t.i.d.) in 77 patients with stable angina pectoris (mean ± SD)

Parameter	Trapidil			ISDN			Trapidil vs. ISDN
	Week 0	Week 6	Week 12	Week 0	Week 6	Week 12	
Primary parameter of efficacy Workload capacity (W·min) Intent-to-treat analysis; n = 95	583 ± 281	759 ± 415 ($p_{0,6} < 0.05$)	883 ± 444 ($p_{0,12} < 0.01$)	555 ± 276	744 ± 372 ($p_{0,6} < 0.05$)	827 ± 361 ($p_{0,12} < 0.01$)	NS
Per-protocol analysis; n = 77	598 ± 278	825 ± 424 ($p_{0,6} < 0.05$)	985 ± 430 ($p_{0,12} < 0.01$)	583 ± 282	806 ± 363 ($p_{0,6} < 0.01$)	896 ± 339 ($p_{0,12} < 0.01$)	NS
Secondary parameter of efficacy Exercise duration (min)	8.0 ± 2.4	9.9 ± 3.3 ($p_{0,6} < 0.05$)	11.2 ± 3.2 ($p_{0,12} < 0.01$)	7.8 ± 2.7	9.8 ± 3.0 ($p_{0,6} < 0.01$)	10.6 ± 2.7 ($p_{0,12} < 0.01$)	NS
Cumulative ST-segment depression (mV)	-0.21 ± 0.51	-0.14 ± 0.45	-0.07 ± 0.34	-0.26 ± 0.39	-0.14 ± 0.27	-0.2 ± 0.34	NS
Angina pectoris attacks/ patient/week	3.8 ± 3.8	2.4 ± 2.5	1.1 ± 1.7 ($p_{0,12} < 0.01$)	3.5 ± 2.6	2.1 ± 3.1 ($p_{0,6} < 0.01$)	1.4 ± 2.0 ($p_{0,12} < 0.01$)	NS
Glyceryl trinitrate use/ patient/week	3.4 ± 3.7	2.1 ± 2.5	1.0 ± 1.4 ($p_{0,12} < 0.01$)	3.4 ± 2.5	2.0 ± 3.1 ($p_{0,6} < 0.01$)	1.2 ± 2.0 ($p_{0,12} < 0.01$)	NS
Double product at 75 W (mmHg × beats/min)	14674 ± 2819	14102 ± 2606	13816 ± 2333 ($p_{0,12} < 0.05$)	14963 ± 3431	13604 ± 2722 ($p_{0,6} < 0.01$)	13695 ± 2782 ($p_{0,12} < 0.05$)	NS
Heart rate at 75 w (beats/min)	123 ± 17.6	121 ± 17.7	119 ± 12.2	122 ± 20.8	116 ± 18.8	115 ± 16.0	NS
Systolic blood pressure at rest (mmHg)	132 ± 18.1	130 ± 18.0	133 ± 18.5	133 ± 15.6	130 ± 17.2	134 ± 17.8	NS
Diastolic blood pressure at rest (mmHg)	82 ± 10.3	83 ± 7.5	83 ± 8.8	84 ± 10.0	83 ± 9.2	85 ± 10.0	NS
Heart rate at rest (beats/min)	77 ± 11.9	79 ± 10.8	82 ± 8.1	76 ± 11.2	76 ± 11.6	76 ± 10.4	NS

$p_{0,6}$ = Week 0 vs. Week 6; $p_{0,12}$ = Week 0 vs. Week 12.
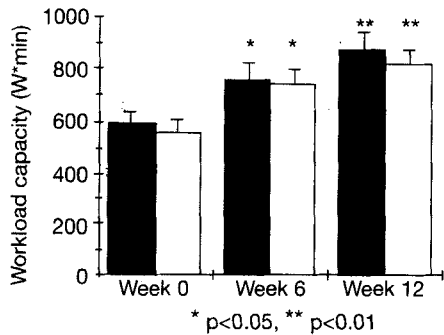*Abbreviation:* NS = not significant. Other abbreviations as in Table I.

FIG. 1 Equivalent increase of the mean (±SEM) workload capacity in 95 patients with stable angina pectoris before and after 6 and 12 weeks of therapy with either oral trapidil (n = 48; 200 mg t.i.d.) or isosorbide dinitrate (ISDN) (n = 47; 20 mg t.i.d.) (intent-to-treat analysis). ■ = Trapidil, □ = ISDN.
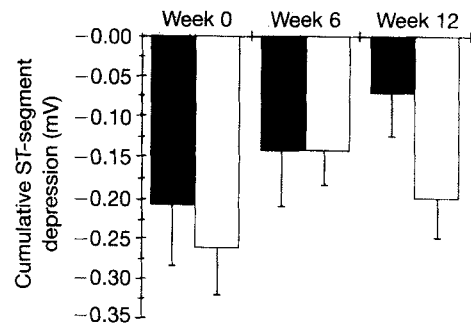

FIG. 2 Cumulative ST-segment depression in 95 patients with stable angina pectoris before and after 6 and 12 weeks of therapy with either oral trapidil (n = 37; 200 mg t.i.d.) or isosorbide dinitrate (ISDN) (n = 40; 20 mg t.i.d.). The decrease was equivalent in both groups. ■ = Trapidil, □ = ISDN.

majority of patients (85% Group 1, 81% Group 2) attained a workload level of 75 to 100 W before verum treatment, the most frequently attained levels after 6 and 12 weeks were 100 to 125 W. In Group 1, levels of up to 150 W and more were attained by 27% compared with 17% in Group 2 (intent-to-treat analysis).

The cumulative ST-segment depression, a measure of total ischemia under exercise ECG, decreased from -0.21 ± 0.51 mV (Week 0) to -0.14 ± 0.45 mV (Week 6) under trapidil treatment and from -0.26 ± 0.39 mV to -0.14 ± 0.27 mV under ISDN treatment (Fig. 2 and Table II). At Week 12, a further decrease to -0.07 ± 0.34 mV occurred in the Group 1, whereas an increase to -0.20 ± 0.34 mV was noted in Group 2 compared with the values in Week 6. The overall reduction was 67% in Group 1 and 23% in Group 2. There was no statistically significant difference between the groups.

The double product is an efficacy parameter used to estimate the capacity of the patient to withstand physical stress. A decrease of the double product at 75 W was apparent in both study groups (Table II).

Blood pressure and heart rate at rest before and after 6 and 12 weeks of verum treatment are listed in Table II. In both groups, systolic and diastolic blood pressure remained unchanged throughout the study. Heart rate at rest slightly increased in Group 1 (NS), whereas the increase during exercise was less pronounced after 6 and 12 weeks of treatment compared with baseline, resulting in a decreased double product.

The weekly anginal attacks were reduced significantly to the same extent in both groups during verum treatment (Table II). In Group 1 patients showed a decrease from 3.8 ± 3.8 (Week 0) to 1.1 ± 1.7 (Week 12) attacks/patient/week (p<0.01) and Group 2 patients showed a decrease from 3.5 ± 2.6 to 1.4 ± 2 attacks/patient/week (p<0.01) (Fig. 3). Hence, the number of GTN uses decreased significantly in both study groups (Table II) from 3.4 ± 3.7 (Week 0) to 1 ± 1.4 (Week 12) uses/week (p<0.01) in Group 1 and from 3.4 ± 2.5 to 1.2 ± 2 uses/week (p<0.01) in Group 2.

Tolerability

For evaluation of tolerability, all 95 patients were included (intent-to-treat analysis). The main adverse events and the reasons for discontinuing the study are listed in Table III. Most of the adverse events were transient and mild to moderate, and the overall tolerability was assessed as good. In Group 1, 11 of 47 (23%) patients had 14 adverse events compared with 14 of 48 (29%) patients in Group 2 with 18 adverse events.

Standard laboratory tests showed no clinically relevant alterations throughout the study. Total cholesterol and triglycerides remained unchanged in both treatment groups whereas low-density lipoprotein cholesterol decreased in Group 1 patients. This effect has to be proven in further studies.

Discussion

A total of 95 patients was randomly allocated either to the trapidil group (Group 1) (48 patients) or to the ISDN group

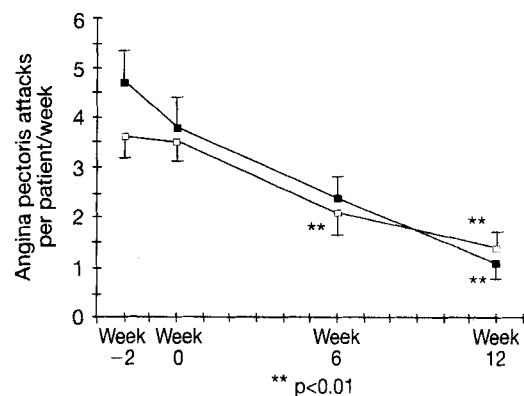FIG. 3 Mean (±SEM) angina pectoris attacks per patient/week in 95 patients with stable angina pectoris before and after 6 and 12 weeks of therapy with either oral trapidil (n = 37; 200 mg t.i.d.) or isorbide dinatrate (ISDN) (n = 40; 20 mg t.i.d.). ■ = Trapidil, □ = ISDN.

TABLE III Occurrence of main adverse events and discontinuations during the study

	Trapidil (n = 47)	Isosobide dinitrate (n = 48)
Number of main adverse events		
Headache	6	16
Gastrointestinal disorders	8	2
Reasons for discontinuation		
Increased anginal attack rate	4	4
Headache and nausea or vertigo	2	0
Severe intercurrent disease	0	1
Not allowed concomitant medication	3	2
Patient's request	2	0

(Group 2) (47 patients) in this double-blind, multicenter clinical trial. Due to the life-threatening potency of angina pectoris attacks and the risk of provoking myocardial infarctions, the double-blind study was planned and performed active-controlled, that is, against the standard therapy with ISDN.

According to the objective of the trial, the change in workload capacity under verum treatment was chosen as the primary parameter of efficacy. If an antianginal therapy is successful, a significant increase in workload capacity is to be expected. Moreover, the secondary efficacy variables as to exercise duration, ST-segment depression, number of anginal attacks, GTN consumption, double product at 75 W, and blood pressure and heart rate are also well accepted to prove the effectiveness of antianginal therapies. In general, the methodology used in this study corresponds to the guidelines referred to in the literature.[14]

To avoid a nitrate tolerance development, a medium dosage of ISDN (20 mg t.i.d.) in a plain release formulation was chosen, with a nitrate-free interval during the night. A nitrate tolerance develops especially when high doses of nitrates are given once daily in a sustained release formulation or when a short dosage interval is used without a nitrate-free interval. The resulting constant nitrate plasma level leads to the attenuation of the anti-ischemic effect.[15] Kleist *et al.*[16] compared the antianginal efficacy of 20 mg ISDN t.i.d. (plain release) with that of 120 mg ISDN once daily (sustained release). The anti-ischemic effect in the evening was significantly stronger with the thrice-daily than with the once-daily regimen. Furthermore, several studies with an ISDN dosage of 20 mg t.i.d. (plain release) found no development of a nitrate tolerance.[17, 18]

One of the pharmacologic mechanisms of nitrate tolerance development that have been discussed is the exhaustion of sulfhydryl (SH) groups. Nitric oxide (NO) requires the SH groups to produce S-nitrosothiols which itself activates the guanylate cyclase and therefore causes the vasodilation.[15] Another mechanism could be the increased vascular superoxide production found in nitrate tolerance.[19] Furthermore, the sympathetic counterregulatory mechanism as well as an activation of the renin-angiotensin system could lead to the attenuation of the antianginal effect of nitrates.[15]

The antianginal therapy with trapidil or ISDN was proven to be effective over the entire period of observation in both treatment groups. The significant increase in workload capacity (52% increase with trapidil and 49% increase with ISDN) is comparable to the results of other studies. Martines and Restori[13] compared the antithrombotic effects of trapidil and acetylsalicylic acid (ASA) in 100 patients with stable angina pectoris. They found an increase in workload capacity of 94% in the patients receiving trapidil, which was significantly higher than in those receiving ASA (54%). LoGiudice *et al.*[12] compared the antianginal efficacy of trapidil and verapamil in 30 patients with chronic ischemic heart disease. After 30 days of therapy, the workload capacity increased significantly by about 40% in the trapidil group whereas the increase in the verapamil group was not significant. The 1-year follow-up of these patients showed a further increase in workload capacity of 27% in the patients receiving trapidil after 3 months.[4]

As to changes in secondary efficacy variables, beneficial effects again became obvious in both treatment groups. Even in Group 1, a further decrease of the cumulated ST-segment depression on exercise ECG after 12 weeks of therapy could be demonstrated, whereas in Group 2 the development of a nitrate tolerance could not be excluded.

The double product at a workload of 75 W decreased in both treatment groups during therapy. Circo *et al.*[4] found a significant decrease of the double product after 3 and 12 months of therapy with trapidil (100 mg t.i.d.) in 27 patients, and Martines and Restori[13] found an equal decrease after 4 weeks in 100 patients. Clinical trials with ISDN have also proven a significant decrease of the double product after therapy.

At rest, blood pressure and heart rate during trapidil therapy remained nearly unchanged in this as well as in other clinical studies.[4, 11, 13]

The incidence of angina pectoris attacks per week decreased in the mean by 71% with trapidil and by 60% with ISDN. Correspondingly, the frequency in the use of GTN also decreased significantly. Again, these results are comparable with those achieved in other trials with trapidil or ISDN.[11, 12] No attenuation of the antianginal effect of the two therapy regimens was detected.

With respect to tolerance and safety, most of the reported symptoms were temporary and ceased in the further course of treatment. All adverse events were known in the profiles of both trapidil and ISDN and might have only minor influence on the patients' well-being. In a postmarketing survey study, the overall incidence of adverse events for trapidil was 3.8%.[20]

Conclusion

The results of this study show that the antianginal efficacy of oral trapidil therapy 200 mg t.i.d. is equivalent to isosorbide dinitrate therapy 20 mg t.i.d. (plain release). Both drugs produced marked anti-ischemic effects and contributed to an improvement of the patients' quality of life. Further studies should confirm the antianginal efficacy of trapidil.

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