The effects on exercise tolerance of a new transdermal therapeutic system containing nitroglycerine, in patients with stable angina pectoris

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In two randomized, double blind, placebo-controlled, within-patient, studies, the effects of 4 doses of a new transdermal therapeutic system containing nitroglycerin (TTS-NTG) were studied in a total of 15 patients with stable exercise-induced angina pectoris. A single 24-hour application of TTS-NTG 10 cm², TTS-NTG 20 cm² and TTS placebo (1st study: 6 patients) and of TTS-NTG 40 cm², TTS-NTG 80 cm² and TTS placebo (2nd study: 9 patients) was applied on 3 different days, and a symptom-limited cycloergometric exercise test was performed 3, 12 (only in the 2nd study) and 24 hours after the application of each treatment.

In comparison with placebo, the doses tested in the 1st study induced, at the 3rd hour post-dosing, a decrease in standing systolic blood pressure and an improvement in exercise tolerance which, however, were not statistically significant while the effects at the 24th hour were similar to those of placebo. In the 2nd study, in comparison with placebo, both TTS-NTG doses induced, 3 hours post-dosing, a significant decrease in both lying and standing systolic (P < 0.01) blood pressure at rest, and a significant (P < 0.01) improvement in exercise tolerance throughout the 24 hours of application.

It is concluded that, in patients with exercise-induced angina pectoris due to coronary artery disease, a single application of TTS-NTG 40 cm² or 80 cm² results in a 24-hour increase in exercise tolerance.

Introduction

An advance in the cutaneous administration of nitroglycerin has been made with the development of controlled release transdermal systems.

The transdermal therapeutic system of nitroglycerin (TTS-NTG) consists of a self-adhesive plaster having an internal reservoir, from which nitroglycerin diffuses towards the skin at a constant rate passing through a microporous membrane. It has been shown that the bioavailability of the drug is 75% and that steady-state concentrations of nitroglycerine are reached 2 hours after application of the plaster. Only slight, statistically non-significant, fluctuations occur in the plasma concentrations during the following 24 hours[1,2].

Some clinical reports have also provided preliminary information on the activity of TTS-NTG in stable[3-5] and unstable[6] angina pectoris. As well, several field studies[7-9], performed on approximately 40 000 patients, have shown the anti-anginal effectiveness of TTS-NTG in terms of a reduction in the number and severity of anginal attacks and of a reduction in NTG consumption. Against these positive results, some papers have been published in which no significant difference in improving exercise tolerance has been shown when the therapeutic system described above[10] and other NTG plasters currently available[11,12], were compared with placebo.

In order to contribute further reliable data, we tested, in two randomized, within-patient, placebo-controlled, double blind studies, performed on patients with coronary artery disease and severe exercise-induced angina pectoris, the antianginal activity of 4 doses of TTS-NTG; namely TTS-NTG 10 cm², 20 cm² (1st study), 40 cm² and 80 cm² (2nd study), releasing 5 mg, 10 mg, 20 mg and 40 mg of nitroglycerin over 24 hours, respectively.
Methods

TRIAL DESIGN

Two randomized, within-patient, double blind, acute studies, each comparing two doses of TTS-NTG (1st study: TTS-NTG 10 and 20 cm²; 2nd study: TTS-NTG 40 and 80 cm²) and placebo (TTS identical in appearance but containing no NTG) were carried out. In each study, treatments were given according to a 3 × 3 latin square design and double blindness was maintained by using the double-dummy technique.

Patients aged less than 70 years with chronic ischaemic heart disease documented by coronary artery angiography and a typical clinical picture of stable exercise-induced angina pectoris were to be admitted to the study. Patients with angina at rest, recent or anterior myocardial infarction, contraindications to the use of nitrates or to the performance of exercise test were, on the other hand, excluded.

EXPERIMENTAL PROCEDURE

After any previous anti-anginal treatment had been discontinued and after having obtained the patients' informed consent to the study, the stability of angina pectoris was evaluated through the performance of 4 exercise tests, carried out at the same hour of the day on 4 different days during the week preceding the start of the trial. Reproducibility was considered good when the variability in exercise duration among the tests was ≤ 15%. This preliminary phase was considered important for the development of the study as it allowed for the removal of all the conditions of variability that could not be controlled by the design of the experiment itself. In particular, the patients were instructed to recognize and define anginal pain, were made familiar with the laboratory staff and equipment, and were questioned about any episodes of angina at rest.

Those patients who showed good reproducibility in the exercise tests and who did not experience episodes of angina at rest, were admitted to the study.

Systems were applied at 7:00 a.m. on days 1, 3 and 5 and exercise tests performed at 10:00 a.m. (3rd hour post-dosing) and at 7:00 a.m. of the following day (24th hour post-dosing), after which the patches were removed. In the 2nd study an exercise test was also performed at 7:00 p.m. (12th hour post-dosing).

All patients were kept hospitalized during the study.

Multistage symptom-limited exercise tests were performed in a sitting position on a bicycle ergometer (Siemens) with electromagnetic brake, starting with a 30 W workload which was increased by 30 W every 3 minutes.

Exercise test end points were: typical anginal pain of moderate severity, horizontal or downsloping S-T segment depression > 2 mm, lasting ≥ 0.08 s from J point in the lead in which the most prominent alterations occurred during all preliminary tests, lack of systolic blood pressure increase in two consecutive steps, excessive blood pressure increase (> 200/100 mmHg), marked dyspnoea, symptoms of cerebral hypoxia, life-threatening arrhythmias and physical exhaustion.

A 12-lead ECG was recorded at rest, in the last 20 s of every minute during exercise and during a 6-minute recovery period. Three leads were also monitored continuously during the entire period of exercise and recovery. Blood pressure measurements were made by a mercury sphygmomanometer immediately before exercise and were taken without knowing the results of previous exercise tests. During exercise, B.P. was measured in the last 20 s of every minute using the same cuff on the same arm. Heart rate was measured from the ECG.

The laboratory temperature was kept between 22° and 24°C.

STATISTICAL ANALYSIS

In both studies, results were analysed using the analysis of variance for latin square design, followed by orthogonal comparisons.

Patients

A total of 15 male in-patients, 49 to 65 years of age, were enrolled: 6 in the low-dose (1st study) and 9 in the high-dose (2nd study) protocol.

All had suffered from stable exercise-induced angina and had a pathological coronary angiography (more than 50% reduction of the diameter of at least two vessels). Five patients had suffered a previous myocardial infarction.

None of these had suffered from angina at rest, anterior myocardial infarction, any other myocardial infarction over the previous three months, arterial hypertension, heart failure, atrioventricular or intraventricular conduction defects, ventricular arrhythmias Lown class III or IV, or anaemia (RBC < 3 500 000 mm⁻¹).

All patients gave informed consent.

Results

Since there was no effect over time for any of the
evaluation parameters, as revealed in the analysis of variance by the lack of significant changes among the periods regardless of the treatment, data is given according to the dose, irrespective of the sequence.

RESULTS AT REST

In the low-dose protocol (Table 1), both TTS-NTG doses induced, 3 hours post-dosing and in comparison with placebo, a decrease in lying (6-7 and 9-2 mmHg on average, for TTS 10 and for TTS 20 cm², respectively) and standing (10-0 and 11-7 mmHg on average) systolic blood pressure which were not statistically significant; the effects at the 24th hour were similar to those of placebo.

On the other hand, in the high dose study (Table 1) both active TTS-NTG doses induced, in comparison with placebo, a significant decrease in both lying and standing systolic (P < 0-01) blood pressure, at the 3rd hour post-dosing, but not at the 24th hour. The heart rate did not change.

RESULTS DURING EXERCISE

In the low-dose study, (Fig. 1), three hours post-dosing the exercise duration was 218-3 ± 110-7 s after placebo and 273-3 ± 168-0 s (+25%) after TTS-NTG 10 and 20 cm², respectively (difference not significant), while at the 24th hour it was 240-0 ± 160-7 s after placebo and 233-3 ± 126-5 and 260-0 ± 167-2 s after the two NTG doses. Furthermore at the 3rd hour, mean values of total work performed were higher on both TTS-NTG doses than on placebo (difference not significant), while, at the 24th hour, values after active patches were very close to those after placebo.

In the 2nd study (Fig. 2), in comparison with placebo, the duration of exercise increased by 70% (from 291-6 ± 71-1 to 496-1 ± 128-3 s), 63% (from 215-0 ± 35-0 to 350-0 ± 68-1 s) and 22% (from 270-0 ± 63-3 to 328-3 ± 54-8 s) at 3, 12 and 24 hours, respectively, after TTS-NTG 40 cm², and by 94% (from 291-6 ± 71-1 to 566-6 ± 113-6 s), 90% (from 215-0 ± 35-0 to 407-5 ± 72-5 s) and 35% (from 270-0 ± 63-3 to 365-0 ± 84-9 s) at 3, 12 and 24 hours, respectively, after TTS-NTG 80 cm².

There was an even higher rise in total work performed, which increased by 147% (from 1191-1 ± 462-3 to 2943-3 ± 1243-9 Kpm), 129% (from 722-5 ± 205-3 to 1656-6 ± 555-9 Kpm) and 33% (from 1090-0 ± 372-2 to 1450-0 ± 369-5 Kpm) at 3, 12 and 24 hours respectively after TTS-NTG 40 cm², and by 207% (from 1191-1 ± 462-3 to 3660-0 ± 1335-6 Kpm), 184% (from 722-5 ± 205-3 to 2055-0 ± 619-4 Kpm) and 61% (from 1090-0 ± 372-2 to 1755-8 ± 670-4 Kpm) at the same times after TTS-NTG 80 cm². The increase in duration of exercise and total work performed induced by both doses was significant (all P < 0-01) at all times of observation.

In comparison with placebo, both TTS-NTG doses significantly increased (Table 2) peak exercise heart rate (P < 0-01 at all times of observation) and peak exercise systolic blood pressure (P < 0-01 at 3 and 12 hours post-dosing) as well as peak exercise pressure-rate product (P < 0-01) at 3 and 12 hours post-dosing. For all the evaluation parameters, both at rest and during exercise, no statistical difference was found between the two active TTS-NTG doses.

Exercise end-points are reported in Table 3. Dur-

<p>| Table 1  | Resting HR and systolic blood pressure mean values (± SD) in lying and standing position |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Hour</th>
<th>TTS placebo</th>
<th>TTS-NTG 10 cm²</th>
<th>TTS-NTG 20 cm²</th>
<th>TTS placebo</th>
<th>TTS-NTG 40 cm²</th>
<th>TTS-NTG 80 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lying</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>3rd</td>
<td>70-6 (14-1)</td>
<td>70-3 (14-1)</td>
<td>71-0 (13-1)</td>
<td>73-7 (16-8)</td>
<td>72-3 (16-0)</td>
<td>71-1 (11-0)</td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>70-3 (8-4)</td>
<td>76-6 (15-4)</td>
<td>73-3 (10-3)</td>
<td>71-5 (13-0)</td>
<td>74-7 (12-6)</td>
<td>73-5 (10-6)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>3rd</td>
<td>150-8 (6-6)</td>
<td>144-1 (10-6)</td>
<td>141-6 (14-7)</td>
<td>143-8 (20-8)</td>
<td>131-1 (20-1)***</td>
<td>123-8 (13-4)***</td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>142-5 (14-0)</td>
<td>146-6 (8-1)</td>
<td>147-5 (9-8)</td>
<td>138-8 (15-3)</td>
<td>136-6 (17-5)</td>
<td>131-1 (13-1)</td>
</tr>
<tr>
<td><strong>Standing</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>3rd</td>
<td>74-8 (16-9)</td>
<td>70-3 (16-8)</td>
<td>76-6 (10-2)</td>
<td>73-3 (15-7)</td>
<td>75-6 (18-9)</td>
<td>72-4 (12-2)</td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>72-0 (12-4)</td>
<td>81-0 (14-1)</td>
<td>79-5 (11-1)</td>
<td>72-3 (12-3)</td>
<td>73-5 (13-9)</td>
<td>74-6 (11-3)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>3rd</td>
<td>150-8 (12-0)</td>
<td>140-8 (9-7)</td>
<td>139-1 (18-2)</td>
<td>138-3 (19-8)</td>
<td>122-7 (21-8)***</td>
<td>118-3 (16-7)***</td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>142-5 (7-5)</td>
<td>145-0 (11-8)</td>
<td>136-6 (11-8)</td>
<td>133-3 (15-8)</td>
<td>131-1 (18-1)</td>
<td>125-0 (11-1)</td>
</tr>
</tbody>
</table>

** P < 0-01 = in comparison with placebo.
Figure 1 Low-dose study: duration of exercise and total work performed. Values given as mean ± SEM.

Table 2 Peak heart rate, peak systolic blood pressure and pressure-rate product mean values (± SD), observed with the 3 treatments in the high-dose study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatments</th>
<th>TTS placebo</th>
<th>TTS-NTG 40 cm²</th>
<th>TTS-NTG 80 cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>3rd</td>
<td>115.1 (16.1)</td>
<td>122.5 (15.2)**</td>
<td>124.8 (12.6)**</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>120.5 (13.5)**</td>
<td>121.8 (6.8)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>129.4 (15.8)**</td>
<td>122.5 (15.2)**</td>
<td>124.8 (12.6)**</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>3rd</td>
<td>166.1 (18.5)**</td>
<td>174.1 (17.4)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>184.1 (20.5)**</td>
<td>174.1 (17.4)**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>166.1 (22.0)</td>
<td>168.8 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Pressure-rate product</td>
<td>3rd</td>
<td>18918 (3355)</td>
<td>22705 (3006)**</td>
<td>24666 (4583)**</td>
</tr>
<tr>
<td></td>
<td>12th</td>
<td>19446 (2639)</td>
<td>22605 (3535)**</td>
<td>21705 (2725)**</td>
</tr>
<tr>
<td></td>
<td>24th</td>
<td>18679 (3329)</td>
<td>19972 (3143)</td>
<td>20493 (2566)</td>
</tr>
</tbody>
</table>

**P > 0.01 in comparison with placebo.
Effects of exercise tolerance

Duration of exercise

3rd hour

12th hour

24th hour

Total work performed

3rd hour

12th hour

24th hour

**P < 0.01 in comparison with placebo.

Figure 2 High-dose study: duration of exercise and total work performed. Values given as mean ± SEM.

ing placebo treatment, all patients stopped exercise because of moderate angina and ischaemic S-T depression while on TTS–NTG there was a tendency to stop because of physical exhaustion, particularly at the 3rd and 12th hour post-dosing and with the highest dose.

TOLERABILITY

Four out of 6 patients in the 1st study and all patients in the second complained of headache of mild or moderate severity.

Discussion

It is not fully known how nitrates improve exercise tolerance in patients with angina pectoris.[14] Nitroglycerin-induced venodilation seems to be maximal even at low plasma levels while arterial dilation seems to be positively related to plasma nitroglycerin levels without apparent plateau in a large dose range[15]. It is likely that during exercise a reduction in both preload (with an increase in venous pooling and a consequent reduction in venous return and thus
Table 3  Exercise end-points

<table>
<thead>
<tr>
<th></th>
<th>1st study (6 patients)</th>
<th>2nd study (9 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TTS placebo</td>
<td>TTS-NTG 10 cm²</td>
</tr>
<tr>
<td></td>
<td>3rd hour 24th hour</td>
<td>3rd hour 24th hour</td>
</tr>
<tr>
<td>S-T segment</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>depression ≥ 2 mm</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Moderate angina +</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>S-T segment</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>depression ≥ 2 mm</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Physical exhaustion</td>
<td>—</td>
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</tr>
</tbody>
</table>

in cardiac dimensions and wall stress) and afterload (with a consequent reduction in wall stress) may occur during nitroglycerin therapy, leading to a rise in exercise duration, maximal workload and total work performed.

In our first study, low nitroglycerin doses, namely TTS-NTG 10 and 20 cm², induced, in comparison with placebo, an improvement in exercise tolerance only at the 3rd hour post-dosing, which possibly would have reached statistical significance if more patients had been studied. On the other hand an efficacy lasting over 24 hours has been proved in the 2nd study using two higher doses and the lack of clinical and statistical difference between them, suggests that TTS-NTG 40 cm² seems to be the most suitable dose for our patient population. It is not easy to explain the negative results obtained, in our study, with the two low doses, which, while they confirm the data obtained by Crean[10], are not in line with those obtained by other authors.[3-6] It has to be stressed that all patients enrolled in our studies were affected by severe angina pectoris as shown by the fact that most of them stopped the exercise test at the second step during placebo treatment and this could account for the different results obtained in different studies. Given the current state of knowledge, other explanations are difficult to give. The hypothesis about the existence of different haemodynamic conditions in different patients[4] which could condition the individual response to low doses of nitrates and therefore the results of different studies, is thought-provoking but it still has to be confirmed by reliable clinical data.

Another important point emerging from our study is that, at the 24th hour post-dosing, a decrease in exercise tolerance and a tendency for systolic blood pressure to return to basal levels were observed, particularly when comparison is made with the 3rd hour.

Such a phenomenon might be due to a decrease in plasma concentrations of nitroglycerin, inadequacies in methodological procedures or haemodynamic counter-regulatory mechanisms. Plasma nitroglycerin levels after TTS-NTG were not measured in our studies, mainly because of the many difficulties in the sampling and analytical procedures, which may be possible sources of error. However, according to the literature, plasma nitroglycerin concentrations are directly related to the size of the drug-releasing area of the system, and seem to remain nearly constant as long as the system is in contact with the skin.[2] This published data suggests that the results obtained in our study are not due to the pharmacokinetics of the drug but to something else.

Methodological procedures are particularly important in the evaluation of antianginal drugs and every care was taken to ensure the reliability of the results of our studies which were within patient, double blind and placebo-controlled. As even the placebo treatment was randomized in the two latin square designs it is unlikely that the effects observed during TTS-NTG administration were conditioned by a training effect due to multiple exercising.[16]

As far as the haemodynamic effects are concerned, it is well documented in the literature[2] that the linear increase in plasma nitroglycerin concentrations with
increasing doses, does not result in a linear increase in all haemodynamic effects. Only the decrease in systolic blood pressure in the passively tilted position seems to be dose-related. In our study the effects of TTS-NTG on systolic blood pressure, at rest, both in lying and standing positions, were particularly evident at the 3rd hour post-dosing, but not at the 24th hour. This phenomenon, probably due to a sympathico-adrenal counter-regulatory mechanism\cite{17} that opposes the arterial vasodilating effect of nitroglycerin, could explain why the increase in exercise tolerance evens out at a lower level at the 24th hour. Venous dilation alone is therefore probably responsible for the increase in exercise tolerance at the time, while the decrease in peripheral resistance and the dilation of coronary arteries, as shown by the reduction in systolic blood pressure and the increase in pressure-rate product respectively, may play an important role during the first hours postdosing.

In conclusion, the findings of this study show that a single application of TTS-NTG 40 cm$^2$ or 80 cm$^2$ brings about a long-lasting increase in exercise tolerance in patients with severe stable angina pectoris induced by exercise, but whether this effect is sustained over time remains to be tested in long-term clinical trials.

References


