Exercise capacity with transdermal nitroglycerin in patients with stable angina pectoris

M. A. B. Naafs*, A. C. de Boer*, R. W. Koster†, C. W. Klazen† and A. J. Dunning†

* Municipal Hospital Bergweg, Rotterdam and † Academic Medical Center, Amsterdam, The Netherlands

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Transdermally delivered nitroglycerin (TTS-NTG) through a rate-controlling membrane yields stable blood levels for 24 h. We studied the effect of TTS-NTG (25 mg per 10 cm²) on exercise induced angina in 10 patients with stable angina pectoris, all in NYHA class III, who were not under treatment with other cardiac drugs.

In a pre-study exercise test, all patients had angina pectoris and more than one mm ST depression. The study was placebo controlled and double blind with a randomized cross-over. Exercise tests were carried out on a treadmill according to the Bruce-protocol, 12 to 16 h after administration of TTS-NTG or of an identical placebo. After a 48 h wash-out period, the procedure was repeated after application of a plaster with the alternative content. A significant improvement was seen on TTS nitroglycerin compared with placebo in the total duration of exercise (7-2±3-6 min (mean±SD) vs 6-2±3-8 min; P<0-002). In 7 patients, the time to onset of angina was extended by TTS nitroglycerin. Maximal ST depression (lead V4 and V6) was significantly lower on TTS nitroglycerin (1-85±1 mm) compared with placebo (2-2±1 mm; P<0-05). It is concluded that 12 to 16 h after administration, transdermally delivered nitroglycerin improves exercise capacity and reduces maximal ST depression in patients with stable angina.

Introduction

Since the first description of its use by Murrell1, nitroglycerin has proved to be effective in the acute therapy of angina pectoris and congestive heart failure2-3. Although the sublingual route offers quick relief of symptoms, the duration of action is limited by rapidly diminishing blood levels4-5. The clinical efficacy of the longer-acting oral or buccal preparations is conditioned both by the variability of the individual response, probably due to variations in absorption and rapid first-pass hepatic metabolism5-6.

Nitroglycerin ointments have proven to be of clinical benefit, but the application is inconvenient and produces variable plasma levels depending on the skin area over which a given dose is spread7-8.

To overcome these limitations, a transdermal therapeutic system for the administration of nitroglycerin has been developed and tested in human volunteers. This application system has been shown to yield stable nitroglycerin plasma concentrations over a 24-h period9-12. It was the objective of our study to establish the clinical efficacy of the nitroglycerin transdermal therapeutic system (NTG-TTS)† in patients with stable angina pectoris.

Patients and methods

NTG-TTS

The NTG-TTS tested was a self-adhesive system with a contact area of 10 cm², and with an internal reservoir containing 25 mg nitroglycerin, adsorbed on silicone and provided with a rate controlling membrane. Systems identical in appearance but without active drug were used as placebo.

STUDY DESIGN

The design of the study was double-blind, randomized cross-over. Patients were randomized to treatment with a TTS-system, containing 25 mg of nitroglycerin or placebo, that was applied to the lateral chest. After 12-16 h, a symptom-limited
Table 1  Resting heart rate and blood pressure in the two phases of the study

<table>
<thead>
<tr>
<th></th>
<th>TTS nitroglycerin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>83.4±20.7</td>
<td>78.7±15.0</td>
</tr>
<tr>
<td>BP syst (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td>167.5±13.6</td>
<td>169.0±18.8</td>
</tr>
<tr>
<td>standing</td>
<td>162.8±8.3</td>
<td>164.4±13.1</td>
</tr>
<tr>
<td>BP diast. (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>supine</td>
<td>92.5±6.8</td>
<td>94.5±10.4</td>
</tr>
<tr>
<td>standing</td>
<td>91.1±8.3</td>
<td>93.9±8.9</td>
</tr>
</tbody>
</table>

No statistical significance in all data.

Table 2  Heart rate and double product at symptom limited exercise in 10 patients with stable angina treated with TTS-nitroglycerin or placebo

<table>
<thead>
<tr>
<th></th>
<th>TTS nitroglycerin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>135.3±18.2</td>
<td>138.6±15.5</td>
</tr>
<tr>
<td>Double product at symptom limited exercise (x 10³)</td>
<td>25.4±5.1</td>
<td>26.3±5.3</td>
</tr>
</tbody>
</table>

No statistical significance in all data.

PATIENTS

Ten patients (7 males and 3 females) with a mean age of 58 years (range 46–73) with stable angina pectoris were studied. All patients were in NYHA class III. Angina pectoris in all patients was documented by a positive exercise test with both typical symptoms of angina and ST depression of more than 1 mm. The history of angina pectoris ranged from 3 to 48 months (mean 14.5 months). Two patients had a myocardial infarction at least 3 months before the study. Seven patients were on beta-blocker therapy, one patient also took nifedipine. Two patients were on oral long-acting nitrates. Beta-blocker therapy was discontinued at least 48 h prior to the study period, nifedipine and long-acting oral nitrates at least 24 h. Sublingual nitroglycerin was not given at least 1 h before the exercise tests. All patients gave informed verbal consent.

STATISTICAL ANALYSIS

The Student t-test for paired data was used. A difference of P<0.05 was considered significant.

Results

The results of heart rate and blood pressure at rest in the two phases of the study are shown in Table 1. There was no significant difference in either heart rate or blood pressure between the two phases of the study. The heart rate and the double product on symptom limited exercise is shown in Table 2. There was no significant difference in heart rate and double product on symptom limited exercise between the two phases of the study.

The total duration of exercise and the maximal ST depression is shown in Figs 1 and 2, respectively. The total duration of exercise was significantly longer after treatment with transdermal nitroglycerin compared with placebo (P<0.002). In addition, the maximal ST depression (sum of lead V4 and V6) was significantly less after treatment with transdermal nitroglycerin (P<0.005). In 2 patients exercise induced angina was prevented by both placebo and TTS nitroglycerin, although they had a positive exercise test in the past. In 1 patient angina developed after 3 min of exercise in the TTS nitroglycerin phase of the study, but no angina occurred on treatment with placebo, but the exercise had to be stopped after only 2 min because of exhaustion. When these 3 patients were excluded,
the remaining 7 patients had anginal pain in both exercise tests. In those 7 patients angina pectoris occurred after $4.36 \pm 2.32$ min of exercise on placebo, and after $5.64 \pm 2.72$ min on TTS nitroglycerin ($P<0.001$) (Fig. 3). When the maximal ST segment depression was compared at the same value of heart rate (120 beats min$^{-1}$), no significant differences were observed between placebo- and active treatment (Fig. 4). However, when ST segment depression was compared at a same level of exercise for both tests, treatment with nitroglycerin was shown to result in less ST segment depression ($P<0.01$) (Fig. 5).

**SIDE EFFECTS**

On placebo, 1 patient complained about a slight local erythema after removal of the system. On TTS nitroglycerin 1 patient had moderate headache and 1 patient called for medical help because of nausea, vomiting and headache. Both patients continued with the study. Both were not used to
Discussion

The clinical efficacy of nitroglycerin is limited by its shortness of action, mainly by first-pass metabolism in the liver, and by a variable absorption. These limitations in the use of sublingual nitroglycerin, long-acting buccal or oral nitrates and nitroglycerin ointments, have led to the development of transdermal nitroglycerin delivery systems. These systems release the drug at a constant rate by means of a reservoir, with either a rate controlling membrane, or by adsorption of the drug to a polymer gel. Human pharmacological studies by Müller et al.\(^{12}\) showed that these systems yield stable plasma levels over a 24 h period. Steady state plasma concentrations of nitroglycerin were reached within 2 h of application of the system. Removal of the system after 24 h resulted in a rapid decline in plasma levels. Additionally, a linear correlation between the transdermal dose and plasma concentrations of nitroglycerin has been reported\(^{12}\). The haemodynamic effects of these transdermal nitroglycerin delivery systems have been well studied in patients with congestive heart failures. Invasive studies in these patients did show that transdermal nitroglycerin reduces pulmonary capillary wedge pressure, and leads to an increase in stroke volume and cardiac output\(^{14,15}\). The anti-anginal effect of these nitroglycerin delivery systems has been studied in only a limited number of clinical trials\(^{16-20}\). Some authors reported a beneficial effect\(^{16-19}\), but this could not be confirmed by others\(^{20}\).

In a short-term study, Schiavoni et al.\(^{17}\) found that transdermal nitroglycerin (100 mg per 20 cm\(^2\)) increased exercise tolerance in patients with angina, and reduced maximal ST depression. The length of action of the transdermal system was reported to be between 24 and 26 h. Similar observations were reported by Thompson\(^{16}\), using a different transdermal device containing 16 mg of nitroglycerin. Reichek et al.\(^{19}\) found that patches with low doses of nitroglycerin (mean 9-5 mg) did not affect exercise tolerance in patients with angina. In contrast, patches with higher doses of nitroglycerin (mean 19 mg) prolonged exercise time 8 h after application of the patch, but the beneficial effect had disappeared by 24 h.

In our study we did not observe a change in resting heart rate during treatment with TTS-NTG. In addition, in agreement with Müller et al.\(^{12}\), we did not find a fall in resting supine blood pressure during TTS-NTG compared with placebo. In our study, a significant improvement was seen in the total duration of exercise and the time of onset of angina pectoris 16 h after the single application of TTS nitroglycerin (25 mg per 10 cm\(^2\)), compared with placebo. No individual patient had better results in any of the parameters monitored on placebo than on TTS-NTG. In regard to the total duration of exercise, 8 of 10 patients improved during the TTS-NTG phase of the study. Maximal ST segment depression was also significantly lower on TTS-NTG.

It can be concluded from our study and the other studies mentioned above, that single application of transdermal nitroglycerin patches is effective prophylaxis of exercise induced angina pectoris. Whether the same holds true for the long-term treatment, remains to be established.

In a 4-week cross-over study, Georgopoulus et al.\(^{18}\) found that NTG-TTS reduced the daily frequency of anginal attacks by 67%, and the daily consumption of nitrates by 63%. However, in a recent clinical trial TTS nitroglycerin given for 1 week did not affect nitroglycerin consumption, exercise tolerance or episodes of ST segment depression\(^{20}\). It is obvious that more long-term studies of continuous transdermal nitroglycerin in the treatment of chronic angina pectoris are needed.

It is concluded that transdermal nitroglycerin delivery systems offer a promising, convenient and well
tolerated approach in the treatment of patients with stable angina pectoris. The clinical efficacy of nitroglycerin in combination with this convenience of use, might ensure patient compliance.

References


Comment on this paper by R. Balcon appears on p. 715 at the end of the paper by Cerri et al.