A double-blind multiple crossover trial evaluating a transdermal nitroglycerin system vs placebo

K. DICKSTEIN AND H. KNUTSEN
Medical Department, Central Hospital in Rogaland, Stavanger, Norway

KEY WORDS: Angina pectoris, transdermal nitroglycerin therapy.

Fifty-six patients with angina pectoris on effort participated in a 28-day study comparing a transdermal nitroglycerin system (TNS) against placebo. The protocol was based on a regular double-blind multi-crossover pattern. The variables recorded included daily sublingual nitroglycerin requirement, daily anginal attack frequency, and a subjective patient evaluation of each day on a visual analog scale. TNS dosage ranged from 10 cm$^2$ (5 mg per 24 h) to 60 cm$^2$ (30 mg per 24 h) based on the patient's dosage prior to commencement of the study. All other medication was continued unchanged. The results demonstrate improvement on active therapy in the patient group using $\geq 20$ cm$^2$ TNS whereas no significant improvement in patients using 10 cm$^2$ TNS was seen. In the higher dose group, the mean number of daily anginal attacks was 2.5 on placebo and 1.4 on active therapy ($P < 0.0001$). Corresponding mean daily sublingual nitroglycerin requirement was 3.6 on placebo and 2.3 on active therapy ($P < 0.0001$). Although TNS therapy was associated with significant improvement in the group using the higher dosage, the results suggest the development of tolerance on active therapy. The possibility of rebound effect and the absence of demonstrable efficacy in the low dose group require further investigation.

Introduction

For over 105 years nitroglycerin has been the mainstay in the management of pain in patients with angina pectoris[1]. Oral nitrate preparations have gained wide acceptance and appear to be both well tolerated and efficacious[2,3]. However, due to hepatic degradation, effective serum concentration is usually achieved via sublingual administration. Since 1948, nitroglycerin ointment has been available and has been shown to be useful in certain clinical settings[4,5]. However, its application is often found to be cumbersome and absorption may be unreliable[6,7].

Transdermal nitroglycerin delivery systems became available for clinical trials in 1979. At our institution we began in 1980 to recommend transdermal nitroglycerin therapy in patients with angina pectoris obtaining satisfactory results. The present double-blind multi-crossover study was set up to examine the clinical efficacy of a transdermal nitroglycerin system (TNS) against placebo.

As our previous clinical experience suggested that transdermal therapy was most effective in patients whose chest pain was responsive to nitroglycerin we decided to limit our study to such patients. We had also formed the suspicion that higher dose therapy was most efficacious and this hypothesis was examined using subgroup analysis.

Methods and materials

PATIENT POPULATION

Sixty patients entered and 56 patients completed the study. There were 39 males and 17 females with a mean age of 64 years (range: 47–85). Inclusion into the study was limited to patients who reported relief of effort related chest pain by the use of nitroglycerin administered sublingually and all patients included in the study had been on TNS therapy for at least one month. The only exclusion criterion was recent myocardial infarction (less than three months).
At entry 27 patients were on 10 cm$^2$ TNS (25 mg), 24 patients were on 20 cm$^2$ TNS (50 mg), 3 patients were on 40 cm$^2$ TNS (100 mg) and 2 patients were using 60 cm$^2$ TNS (150 mg). Two groups were thus identified; 27 patients on low dose therapy (10 cm$^2$) and 29 patients on higher dose therapy (≥20 cm$^2$). The diagnosis of angina pectoris was based on the presence of typical effort related chest pain relieved by rest or administration of sublingual nitroglycerin. The clinical diagnosis of effort angina pectoris was made by at least two independent physicians.

Thirty-eight patients had documented previous myocardial infarction, 19 patients had pathological coronary angiograms, 7 patients had previous coronary bypass surgery and 28 patients had positive stress tests. The mean duration of angina pectoris was 7-2 years (range 1–23). Thirty patients were currently on beta-blocker therapy, 33 on calcium antagonist therapy and 13 used oral long-acting nitrates in addition to nitroglycerin sublingually and transdermally.

Table 1 displays the criteria for diagnosis along with concomitant therapy for the two groups. Both the cardiac history and the extent of concomitant medication imply more advanced disease in the higher dosage group. This is compatible with the observed difference in the severity of angina between the two groups demonstrated during the study (see Table 2).

**MATERIALS**

The transdermal application system used in this trial was developed by ALZA Pharmaceuticals (Palo Alto, California) and produced by Ciba-Geigy. It is designed in the form of an adhesive patch with a surface area of 10 or 20 cm$^2$ containing a nitroglycerin reservoir absorbed to silicone and sandwiched between an outer impermeable membrane that acts occlusively and an inner semipermeable membrane which limits the rate of delivery to the skin. The two sizes contain 25 mg and 50 mg nitroglycerin, respectively, and pharmacokinetic studies indicate that release is sustained and relatively constant with a rate of release on normal skin of approximately 5 mg per 24 h for the 10 cm$^2$ system and approximately 10 mg per 24 h for the 20 cm$^2$ system$^8$. The inner microporous
Table 2  Comparison of the observed differences on active and placebo therapy between the two patient groups

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Anginal Attack Rate</th>
<th>Sublingual Nitroglycerin usage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(mean ± standard deviation)</td>
<td>(mean ± standard deviation)</td>
</tr>
<tr>
<td>Placebo</td>
<td>Active</td>
<td>Difference</td>
</tr>
<tr>
<td>10 cm$^2$ transdermal nitroglycerin ($N = 27$)</td>
<td>1.2 (±1.7)</td>
<td>1.0 (±1.6)</td>
</tr>
<tr>
<td>≥ 20 cm$^2$ transdermal nitroglycerin ($N = 29$)</td>
<td>2.5 (±2.4)</td>
<td>1.4 (±1.4)</td>
</tr>
</tbody>
</table>

membrane has a diffusion rate of approximately 40 μg cm$^{-2}$ h$^{-1}$. Since skin permeability for the nitroglycerin in this delivery system is usually under 25 μg cm$^{-2}$ h$^{-1}$, the rate of absorption will be limited by skin permeability. In patients with exceptionally high skin permeability the rate limiting factor will be the semipermeable membrane. A plasma plateau is generally reached at 1 to 2 h following application, and serum levels are no longer measurable by assays presently available 30 to 60 min following removal of the system[8]. The placebo systems were prepared identically, omitting the inclusion of nitroglycerin in the drug reservoir.

STUDY PROTOCOL

The trial was designed to test the clinical efficacy of transdermal nitroglycerin as compared with placebo. Patients remained on all other medication including oral long acting nitrates during the period of study. Dosage of TNS therapy during the study was identical to the dosage the patients had been using prior to entry.

The design was based on a regular multiple crossover pattern*. During a period of 28 days the patients received active drug for 14 days and placebo for 14 days. The crossover pattern was active therapy for 2 days followed by placebo for 2 days and this pattern was repeated throughout the study, thus permitting 12 crossovers with each patient experiencing 7 periods of active therapy and 7 periods of placebo. At entry, half of the patients were started on active therapy and half on placebo. The patients were unaware of the pattern, but were informed that 14 of the 28 days would involve placebo.

The patients were asked to lead an unchanged life style and to continue to use nitroglycerin sublingually as they had been doing previously. A form was prepared on which the patients could register two efficacy variables on a daily basis: episodes of anginal chest pain and the number of nitroglycerin tablets taken sublingually. In addition, patients were asked subjectively to evaluate each day on a 100 mm visual analog scale with regard to the severity of their angina that day. Ample space for recording side-effects was provided.

STATISTICAL METHODS

The significance of observed mean differences for all the examined variables based on cumulative mean values for 14 placebo days and 14 active days, respectively, was evaluated by means of a one-sided Wilcoxon signed-rank test. Mean differences between the high and low dose patient groups were examined using a two-sided Wilcoxon rank-sum test. Evaluation of the mean differences between the first and second day of the period was based on a two-sided Wilcoxon signed-rank test. Statistical significance was accepted at the 95% confidence level ($P<0.05$).

Results

Patient compliance was excellent. Sixty patients originally entered the study. Fifty-six patients completed the study as per protocol. One patient was excluded who required emergency peripheral embolectomy, one patient was called in for elective coronary bypass surgery, one patient was admitted in connection with an admission to hospital for acute cholelithiasis, and one patient changed his mind the day after inclusion.

The results are demonstrated graphically in Fig. 1. For the group using 10 cm$^2$ TNS no significant
change as regards number of sublingual nitroglycerin tablets taken per day, number of anginal attacks per day or evaluation of anginal pain on a 100 mm visual analog scale was demonstrated. However, marked changes in these 3 variables were seen in the group using \( \geq 20 \text{ cm}^2 \) TNS.

In the group using \( 10 \text{ cm}^2 \) TNS (\( N = 27 \)) the mean number of daily anginal attacks was 1.2 on placebo and 1.0 on active therapy (\( P = 0.07 \)). Corresponding mean daily nitroglycerin requirement was 2.0 on placebo and 1.7 on active therapy (\( P = 0.06 \)). In the group using \( \geq 20 \text{ cm}^2 \) TNS (\( N = 29 \)) the mean number of daily anginal attacks was 2.5 on placebo and 1.4 on active therapy (\( P < 0.0001 \)). Corresponding daily nitroglycerin requirement was 3.6 on placebo and 2.3 on active therapy (\( P < 0.0001 \)). These results are displayed in Table 2. Assessment of the visual analog scale showed no improvement in the \( 10 \text{ cm}^2 \) TNS group (25 mm on placebo and 24 mm on active therapy (\( P = 0.24 \)). However, significant improvement was observed in the \( \geq 20 \text{ cm}^2 \) TNS group (34 mm on placebo and 25 mm on active therapy (\( P < 0.0001 \)). No significant differences between the pattern observed in the \( 20 \text{ cm}^2 \) TNS group and the 5 patients using \( > 20 \text{ cm}^2 \) TNS was found.

Efficacy was defined as the difference between the mean number of anginal attacks daily on placebo vs the mean number of anginal attacks daily on active therapy. The group was subdivided retrospectively and efficacy was evaluated with respect to age, sex, duration of angina pectoris, previous myocardial infarction and previous coronary bypass surgery. No significant associations were found. Concurrent therapy with beta-blockers, calcium antagonists, or long-acting nitrates did not appear to be related to TNS clinical efficacy.

A strong positive correlation between efficacy of TNS and the average number of anginal attacks while on placebo was found. In the 25 patients who averaged over one attack per day, mean efficacy
was found to be 1.4 as compared with 0.0 for the rest of the group ($P < 0.0001$). It should be noted that the mean attack frequency and nitroglycerin requirement were significantly lower for both active and placebo days in the 10 cm$^2$ TNS group as compared with the $\geq 20$ cm$^2$ TNS group (mean attack frequency on placebo was 1.2 for the 10 cm$^2$ group vs 2.5 for the $\geq 20$ cm$^2$ group). This correlation may be of importance in interpreting the response in the low dose group.

Closer examination of Fig. 1 reveals four significant trends. Most striking is a wave pattern for the group using $\geq 20$ cm$^2$ TNS demonstrating improvement in the displayed variables on the first day of active therapy and deterioration on the first day of placebo treatment. In addition, a significant attenuation of efficacy was seen on the second day of active therapy at every crossover ($P < 0.05$), and a significant improvement on the second placebo day was seen at every crossover ($P < 0.01$).

There were no adverse experiences with regard to the intensity of anginal symptoms during this trial and no patients were admitted to hospital due to chest pain. Side-effects were few and tolerance was excellent. However, this study included only patients who had previously been on long-term TNS therapy and therefore the assessment of tolerance may be misleading. Five patients experienced local skin irritation that was managed by varying the TNS application site, 2 patients complained of mild headache and 1 patient reported periodic dizziness. It was not possible to determine whether these side effects occurred only on active therapy.

**Discussion**

This study was designed to test the hypothesis that nitroglycerin applied transdermally can be effective in reducing the attack frequency and sublingual nitroglycerin requirement in patients with angina pectoris on effort.

Only patients reporting nitroglycerin responsiveness were studied and conclusions from the results must be limited to this patient group. Two groups comprised the patient population, 27 patients on low dose therapy and 29 patients on higher dose therapy. It was retrospectively seen that the anginal attack rate on placebo for these 2 groups was quite different which therefore precludes comparison.

We employed a relatively unique trial design and although the results support our hypothesis in the high dose group, interesting patterns were observed that complicate interpretation of the data. It must be emphasized that important questions are raised and although the trial design illuminated these questions, modification of the design is required to provide the answers.

We were attempting to assess the degree of pain in a disease that shows marked individual variation. Such a highly subjective variable does not lend itself to accurate quantification. Although frequent exercise testing may be used to evaluate intervention, this approach involves an artificial setting and many patients with severe angina pectoris find repeated testing unacceptable. In addition the severity of angina exhibits wide variation for the individual patient. The degree of physical activity, emotional stress, concurrent illness and even ambient temperature changes (a well recognized phenomenon among Norwegian patients) may significantly influence the course of the day in this disease.

We decided to record the two most notable daily events in patients with angina pectoris; episodes of chest pain and the sublingual use of nitroglycerin. Although a patient’s interpretation of chest pain and his decision to take nitroglycerin sublingually are subjective, they represent real events of clinical relevance and are valid variables in the evaluation of clinical efficacy. The patients were also asked to record their own subjective evaluation of the severity of their angina daily on a visual analog scale.

In the subgroup using $\geq 20$ cm$^2$ TNS highly significant improvement seems apparent. However, the design permitted observation of four significant patterns that occurred repeatedly throughout the study. Improvement was observed on both the days of changing from placebo to active therapy ($P < 0.001$) and on the second day of placebo therapy ($P < 0.01$). Worsening of symptoms was observed both when changing from active to placebo therapy ($P < 0.0001$) and on the second day of active therapy ($P < 0.05$). These patterns are interesting and emphasize both the strengths and limitations of this study. Although the periodicity of the design permitted these trends to become apparent, no true control baseline is provided and the issue of chronic efficacy remains unanswered. Modification of the trial design by varying the length of periods between crossovers might address these problems more adequately.

Examination of these four patterns more closely suggests an interpretation based on the develop-
have demonstrated sustained effect\cite{9,10}, most investigators have demonstrated short-term efficacy with attenuation during the course of 24 h\cite{11-13}. Although no data is available concerning the timing of anginal attacks in this study the significant attenuation of effect on the second day of active therapy supports the concept that tolerance does indeed develop with the 2 placebo days functioning as a sufficient washout period to permit response on the next crossover to active therapy. Indeed, assuming a certain threshold dosage permitting the development of tolerance in the higher dose group, such a theory could have crucial bearing on the interpretation of the results.

Nitroglycerin’s ability to affect the coronary vasculature (vasodilatation and redistribution of coronary blood flow) does not persist following cessation of therapy. However the effects of chronic therapy on intravascular volume may suggest a mechanism for the development of tolerance. It can be speculated that chronic venodilatation could lead to increases in intravascular capacitance with reduced preload and symptomatic improvement. On the first placebo day such augmented intravascular volume would no longer be compensated for via venodilatation, and increased preload could result in increased angina. Compensatory readjustments of intravascular volume during the first placebo day might partially explain the improvement seen on the second day of placebo therapy. Similarly, the reduction of preload on the first day of active therapy followed by compensatory increases in intravascular volume might explain the observed attenuation of effect on the second day of active therapy, suggesting a mechanism for the development of tolerance.

The marked worsening of anginal symptoms at crossover from active to placebo therapy deserves further attention. Such a pattern can suggest rebound following the development of tolerance. A syndrome of withdrawal symptoms and occasional, but well documented myocardial ischemia has been associated with chronic industrial exposure and considerable attention has been given to this phenomenon in the literature\cite{16-19}. The mechanism of unopposed compensatory vasoconstriction following long-term vasodilatation has been suggested\cite{20} and it was feared that the advent of new long-acting nitrates might lead to a rebound effect in patients with angina pectoris placed on chronic therapy\cite{21}. This has not been observed in clinical practice and although it is routinely recommended to reduce therapy gradually, this is difficult to accomplish practically. Extrapolation from experience following high-dose industrial exposure to the clinical setting may be inappropriate. No patients in this study reported adverse experience in close connection with the actual time of switching the systems. This speaks against a rebound effect when dealing with a drug with a biological half-life of approximately 3 to 5 min\cite{22}. In addition, in the low dose group in this study one would expect some evidence of rebound and no such tendency was observed, although a threshold level is a possibility.

Other considerations might also play an important role. Understandably, such a transdermal delivery system may have a marked placebo effect. However, such effects are usually transient and all patients included in this study had been on chronic therapy. An essential detail is the fact that the second placebo day was associated with significant improvement. This is directly opposite to the pattern observed in studies of the placebo effect i.e. continued therapy shows attenuation of the response\cite{22}.

One could speculate that following the first placebo day after crossover patients experienced increased chest pain and might reduce their activity level the following day. Similarly, following the first day with active therapy patients might be encouraged to be more active thereby contributing to the attenuation of effect on the second day of active therapy.

Notable are the results indicating that 10 cm² TNS provided no significant improvement compared with placebo. In interpreting this finding it must be emphasized that there was a strong positive correlation between efficacy and the average number of anginal attacks while on placebo ($P<0.0001$). The fact that 70% of the patients experiencing an average of one or less anginal attack daily while on placebo were in the low dose group, can understandably serve to underestimate the value of low dose therapy. We were in reality dealing with two distinctly different groups. The patients using ≥20 cm² TNS had over twice the daily attack rate on placebo as compared with the daily attack rate on placebo for the 10 cm² TNS group (2.5 vs 1.2). The low attack rate on placebo in the low dose group thus decreased the likelihood of demonstrating efficacy and caution should be used in drawing conclusions concerning the results in this subgroup. However, most available studies
demonstrate efficacy on higher dosages\cite{23} and the absence of detectable improvement in the low dose group supports these results. We emphasize that the patients continued their use of other anti-anginal agents throughout the study so that no information concerning the use of TNS as monotherapy is provided.

Tolerance was excellent and side-effects were few. However, clinical experience would suggest that headache and local skin irritation occur more frequently in a population not selected in this manner\cite{24,25}.

This study suggests that transdermal nitroglycerin therapy in sufficient dosage is associated with improvement in patients with angina pectoris who experience pain relief by sublingual nitroglycerin administration. However, the data raised some interesting questions and their interpretation is complex. The results are compatible with the development of tolerance on chronic therapy. The contribution of a rebound effect and the absence of demonstrable efficacy in the low dose group require further investigation.

References