Comparison of transdermal nitrate and isosorbide dinitrate in chronic stable angina

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1 The effects of transdermal nitrate (TN) (Transiderm-Nitro TTS, Geigy Pharmaceuticals, one 10 cm² patch daily) and oral isosorbide dinitrate (ISDN) (Sorbitrate, Stuart Pharmaceuticals, 10 mg three times daily) were compared in a group of 20 patients with chronic stable angina pectoris.

2 Treadmill exercise duration was prolonged from a median time of 365 s to 428 s after ISDN ($P < 0.05$), but was unchanged after TN. The difference between the active treatments was not significant.

3 Weekly consumption of glyceryl trinitrate (GTN) increased during treatment with TN from a median value of 5.5 to 6.3 ($P < 0.05$). A decrease was observed after ISDN (7.8 to 3.9, $P = \text{NS}$), and the difference between the drugs was significant ($P < 0.01$).

4 Systolic arterial pressure was significantly lower during the ISDN than during the TN treatment period in both the supine (135 ± 5 vs 128 ± 5 mm Hg; $P < 0.05$) and standing positions (134 ± 5 vs 122 ± 5 mm Hg; $P < 0.05$).

5 No change in weekly attack rate, the degree of ST depression at angina on treadmill testing, or the number of episodes of ST depression recorded during a 24 h period by Holter monitoring was observed after either drug.

6 In this study, an antianginal effect was demonstrated for ISDN but not for TN. It is suggested that the dose of TN may have been inadequate to demonstrate such an effect, and further studies using a higher dose schedule will be required.

Keywords transdermal nitrate oral nitrate comparative trial angina

Introduction

The use of nitrates in the treatment of chronic stable angina is well established (Abrams, 1980; Opie, 1980), although their precise mechanism of action remains unknown (Editorial, 1984). Transdermal absorption of nitroglycerin avoids first pass metabolism in the liver, and a nitroglycerin ointment has been available for many years (Davis & Wiesel, 1955). Such ointments are effective after acute and chronic dosing (Bennett *et al.*, 1983), but have not gained wide acceptance because the ointment has to be covered with an occlusive dressing. New formu-

lations of transdermal nitrate (TN) have been described, which control the release of nitroglycerin from a drug reservoir (Shaw & Urquhart, 1981; Müller *et al.*, 1982). Initial studies have suggested that TN is effective at reducing the frequency of anginal attacks (Garnier *et al.*, 1982; Letzel & Johnson, 1984), and some controlled trials have supported this observation (Georgopoulos *et al.*, 1982; Letzel *et al.*, 1982; Thompson, 1983; Cerri *et al.*, 1984; Hollenberg & Go, 1984; Naafs *et al.*, 1984). More recently, several studies have failed to demonstrate a

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therapeutic effect of TN (Crean *et al.*, 1984; Parker & Fung, 1984; Reichek *et al.*, 1984; Dickstein & Knutsen, 1985).

We have compared the effect of a single daily patch of TN (Transiderm-Nitro TTS, 10 cm² (25 mg total dose), Geigy Pharmaceuticals) with that of isosorbide dinitrate (ISDN) (Sorbitrate, Stuart Pharmaceuticals) 10 mg three times daily in a group of patients with chronic stable angina.

Methods

Patients

Observations were made on 23 patients with a history of chest pain on exertion present for at least three months, with a minimum of five attacks per week and no recent deterioration. Patients were excluded from the study on the following grounds: unstable angina, myocardial infarction in past 3 months, anaemia, severe valvular heart disease, grade 2 or 3 AV block, hypotension, moderate or severe hypertension, migraine, plaster allergy, or any severe concurrent illness. Patients were invited to take part after the protocol had been explained to them and written consent obtained. The trial protocol had been reviewed by the Ethics Committee of the Queen's University of Belfast.

Three patients withdrew from the trial, for the reasons discussed below. The clinical details of the patients who completed are shown in Table 1. Thirteen patients were male. The mean age for the group was 54.5 years (range 39–64) and body weight 74.4 kg (range 47.3–93.8). The duration of angina was 3–84 months (median 18) and the number of attacks in the week prior to the study was 5–70 (median 9). Coronary angiograms were available in 14 patients (70%, see Table 1). A vessel was regarded as stenosed if there was a reduction of 50% or more of the luminal diameter in any one of three planes. Two female patients had normal coronary arteries anatomically. Both had a typical history of anginal pain, and in one (patient 20) catheter tip spasm during angiography reproduced her pain and was associated with ST-segment elevation.

All patients except one were being treated for angina, including 10 with β -adrenoceptor antagonists and 10 with calcium antagonists. All antianginal medication except for glyceryl trinitrate (GTN) was withdrawn 4 days prior to entry into the study. In 13 patients, only trial medication was used during the study. In the remainder, the following drugs were also used throughout the study at constant dose: digoxin (patients 7 and 12), diuretics (patients 4, 5, 7, 9 and 12), warfarin

(patients 7 and 9), cimetidine (patients 5 and 17) and oral salbutamol (patient 4).

Study design

The trial lasted 12 weeks for each patient. In the first 2 weeks, patients were given a dummy patch, dummy tablets and a supply of active GTN for sublingual use. The trial patch and tablets were identical to active TN and ISDN respectively; the patch was to be applied once daily on waking, and the tablets to be taken three times a day. Patients were asked to record any attacks of angina and the number of GTN tablets used, in a diary card. The number of GTN tablets issued at each visit varied and was known to a hospital pharmacist who counted the tablets returned at subsequent visits. Compliance was also assessed at each visit by the number of tablets and patches returned. This phase of the trial was single (patient) blind. For the next 4 weeks, the patients were randomly allocated to receive either active patch and dummy tablets, or dummy patch and active tablets, whilst continuing with a supply of active GTN tablets. This phase of the trial was double-blind. After a placebo washout period of 2 weeks on dummy patch and tablets (single-blind), patients then crossed over to the other active treatment for 4 weeks (double-blind).

Clinical assessment was made before entry into the trial, at the end of each placebo or active treatment period, and in the middle of each active treatment period. At these times, heart rate was measured by palpation of the radial artery over 30 s after 5 min supine rest, and arterial pressure was recorded with a standard sphygmomanometer (diastolic phase IV) in the supine position and after standing for 2 min. Body weight was also recorded at each visit. A full blood count and 24-channel biochemical screening profile was recorded before the trial, and at the end of each placebo and active treatment period. A chest radiograph and 12-lead ECG were recorded before entry to the trial.

Exercise capacity was assessed by treadmill testing before entry into the trial. Lead CM5 was used for recording, and a standard exercise protocol followed until limited by symptoms (Bruce, 1971). All patients experienced chest pain and ST-segment depression of 1.0 mm or more in five or more consecutive complexes 80 ms beyond the J point, except patient 11, who had typical pain but ST depression of only 0.5 mm. The test was repeated 1–3 h after drug administration at the end of each placebo and active treatment period. On each occasion, the following observations were made at peak exer-

Table 1 Clinical details of the 20 patients studied. Sex, age, body weight (kg), angiographic appearance of the coronary arteries (Angio 0 = Normal, 1 = single, 2 = double, 3 = triple vessel disease), ejection fraction (EF%), resting left ventricular end diastolic pressure (LVEDP, mm Hg) and angiographic or ECG appearances. Treatment = transdermal nitrate (TN) or isosorbide dinitrate (ISDN)

No.	Sex	Age (years)	Weight (kg)	First treatment	Angio	EF (%)	LVEDP (mm Hg)	Comments
1	F	49	47.3	TN	2	54	20	Normal ECG
2	F	55	93.7	ISDN	—	—	—	ECG = Left ventricular hypertrophy
3	M	62	78.8	TN	3	53	8	Normal ECG
4	M	52	75.9	ISDN	—	—	—	Old septal infarct
5	M	63	80.0	ISDN	1	49	9	Inferior akinesia
6	M	56	88.1	ISDN	3	12	21	Normal ECG
7	M	64	88.8	TN	—	—	—	Old anterior infarct. Died after trial completed
8	M	43	85.2	TN	3	32	15	Apical aneurysm
9	M	55	80.2	ISDN	2	64	7	Normal ECG
10	F	62	55.4	TN	3	53	6	Normal ECG
11	M	57	69.0	TN	—	—	—	Old inferior infarct
12	F	39	57.6	ISDN	2	78	9	Main stem disease in addition
13	M	62	69.2	TN	3	73	4	Normal ECG
14	F	55	48.5	ISDN	1	91	11	Normal ECG
15	M	60	87.7	TN	—	—	—	Normal ECG
16	F	56	66.8	ISDN	0	60	9	Normal ECG and angiogram but typical history
17	M	51	93.8	TN	2	27	17	Died after trial completed
18	M	51	83.0	ISDN	2	89	18	Main stem disease in addition
19	M	58	79.5	TN	—	—	—	Old inferior infarct
20	F	39	59.2	ISDN	0	74	0	Spasm demonstrated

cise: duration of exercise, systolic arterial pressure, heart rate, double product (systolic pressure $\times$ heart rate), and ST-segment displacement (except in patients 7 and 12, who were continuing digoxin treatment).

A 24 h ECG tape recording was made at the end of each active treatment period for ST-segment analysis. The tape was recorded at 6 cm h^{-1} on a Reynolds Pathfinder II am/fm recorder, and replayed on a Pathfinder Trend System. Sensitivity was set at 0.2 mV cm^{-1} . All episodes of ST displacement of 0.1 mV or more were counted, if they lasted for more than 1 min and were separated from other episodes by more than 10 min. Data from patients 7 and 12 were omitted, as they continued to take digoxin throughout the trial.

The effects of the active drugs were compared using Grizzle's test (Grizzle, 1965) for data which were normally distributed, and Koch's test (Koch, 1972) for those which were not. In each case, the differences from the corresponding pre-treat-

ment values were compared. The effects of the active drug were also measured as the change on treatment from the preceding baseline using Wilcoxon's signed rank test for matched pairs.

Results

The effects of the two active drugs are shown in Table 2. No effect on treadmill exercise duration was observed after TN, whereas the duration was significantly prolonged after ISDN ($P < 0.05$); the difference between the active treatments was not significant. The degree of ST segment depression observed when the treadmill was discontinued was unchanged after either drug, as was the double product at peak exercise. There was no significant change in the reported number of anginal episodes on either treatment. The number of GTN tablets used was greater during the TN treatment period (median 6.3 tablets per week) than during the preceding

Table 2 Effect of transdermal nitrate (TN) and isosorbide dinitrate (ISDN) on various parameters in patients with angina. Median values are shown and $n = 20$ unless otherwise indicated.

	Baseline	TN	Baseline	ISDN
Exercise duration (s)	360	348	365	428*
ST depression at angina (mm) ($n = 18$)	1.8	1.7	1.6	1.4
Double product (mm Hg $\times$ beats min^{-1})	20960	19910	20663	21413
Weekly attack rate	8.8	7.5	7.0	4.3
Weekly GTN consumption	5.5	6.3*	7.8	3.9†
Episodes of ST displacement per tape ($n = 9$)	—	3.0	—	5.0

* = $P < 0.05$ when compared with baseline value† = $P < 0.01$ when compared with the other active treatment

placebo treatment (median 5.5; $P < 0.05$). A reduction was observed during the ISDN treatment period, but this was not significant. There was a significant difference between the two active drugs ($P < 0.01$). Only nine matched pairs of 24 h tapes were available for ST segment analysis due to technical defects in some tapes, and there was no significant difference between the two active drugs in the number of episodes of ST-segment displacement recorded.

In order to detect any trend with time, the two placebo treatment periods were compared (Table 3). Exercise duration was significantly prolonged, and the weekly attack rate significantly reduced in the second (washout) placebo treatment period when compared to the initial (pre-treatment) period, indicating that the exercise tolerance of the patients improved with time. A small reduction in the number of GTN tablets consumed was also observed, but this was not significant.

Systolic arterial pressure was significantly lower during treatment with ISDN than during treatment with TN. In the supine position the pressure after TN was 135 ± 5 mm Hg (mean $\pm$ s.e. mean), whereas after ISDN the pressure was 128 ± 5 mm Hg ($P < 0.05$). In the standing position, the pressures were 134 ± 5 and 122 ± 5 mm Hg respectively ($P < 0.05$). No changes in diastolic pressure or heart rate were observed. Body weight remained unchanged throughout the trial, and no significant changes were observed in any of the haematological or biochemical tests.

The main adverse effects reported are shown in Table 4. These were not subjected to statistical

analysis, as no questionnaire had been used. Headache and tiredness were more common after ISDN, and two erythematous rashes from the plaster were observed. Three patients withdrew from the study. Two patients had increasing angina, one during the initial placebo treatment period, and one during the placebo washout period. The third patient was simply unwilling to keep attending, but reported no adverse affects.

Discussion

The investigation of angina is complicated by the fact that no individual test can be used alone to assess the efficacy of antianginal medication. It is probable that exercise testing and ST-segment tape analysis are more objective indicators of performance than counts of the episodes of chest pain or of the GTN tablets used (Bowles *et al.*, 1984). Even so, exercise duration may increase with time, especially with repeated testing (McGraw *et al.*, 1981; Starling *et al.*, 1984). Such improvement could be due to a training effect, or to spontaneous improvement of the angina with time. In our study, comparison of the two placebo treatment periods (pretreatment and washout, see Table 3) confirmed that the frequency of angina attacks reduced and exercise tolerance improved with time. In any cross-over study, it is important that patients enter both active treatment periods in the same clinical state, but the effect of these changes was minimized by comparing the differences from base-

Table 3 Comparison of the two placebo treatment periods.

	Pre-treatment (initial period)			Washout period		
	Median	Mean	s.e. mean	Median	Mean	s.e. mean
Exercise duration (s)	360	344	29	360*	409	36
Weekly attack rate	10	11	2	4.5**	8	2
Weekly GTN consumption	10	9	2	4.8	9	2

* = $P < 0.05$, ** = $P < 0.01$ for differences between the two periods

Table 4 Side-effects reported during treatment with transdermal nitrate (TN), isosorbide dinitrate (ISDN) or placebo.

	Placebo	TN	ISDN
Headache	0	2	5
Skin rash	2	2	0
Tiredness, depression	2	0	5
Gastro-intestinal	1	3	0

line within each active treatment group, rather than comparison of the absolute values. There was no evidence of any carry-over effects between the two active treatment periods, and the design was balanced, in that 10 patients received TN as first treatment and 10 received ISDN.

We feel therefore that it is reasonable to conclude that in this study an anti-anginal effect has been demonstrated for ISDN, but not for TN. It cannot be said that TN is not effective, as the numbers (especially in the analysis of ST-segments on 24 h tapes) were too small to permit negative conclusions to be drawn. The possibility that higher doses of TN may be shown to be effective also remains (see below).

Studies of the clinical efficacy of TN have given conflicting results. Using the same preparation of TN as in this study, an effect in angina has been demonstrated after single dose (Cerri *et al.*, 1984; Hollenberg & Go, 1984; Naafs *et al.*, 1984; James *et al.*, 1985) and repeated administration (Georgopoulos *et al.*, 1982; Letzel *et al.*, 1982; Hollenberg & Go, 1984). In contrast, other studies have failed to demonstrate a therapeutic effect (Crean *et al.*, 1984; Parker & Fung, 1984; Dickstein & Knutsen, 1985). Similar conflicts of opinion exist about other new formulations of TN (Thompson, 1983; Reichek *et al.*, 1984). However, the new formulations are effective at reducing preload in cardiac failure (Olivari *et al.*, 1983; Rajfer *et al.*, 1984; Sharpe & Coxon, 1984), although high doses may be required (Rajfer *et al.*, 1984).

The possible reasons for the discrepancies have been reviewed (Abrams, 1984a,b). The formulation of TN used in this study contains 25 mg of GTN in a patch of area 10 cm². The diffusion rate is 20–40 µg h⁻¹ cm⁻², and so 5–10 mg of GTN would be released over a 24 h period, which produces a steady state plasma level of about 0.2 ng ml⁻¹ (Müller *et al.*, 1982; Curry *et al.*, 1984). In contrast, sublingual GTN 0.6 mg produces a peak plasma level of 2.3 ± 0.36 ng ml⁻¹ at 2 min after drug administration (Armstrong *et al.*, 1979). Although the therapeutic

range for GTN in plasma has not yet been defined, the lower limit is thought to be 1–1.2 ng ml⁻¹ (Abrams, 1984a). The low nitrate levels produced by the 10 cm² patch may produce venodilation, which is an important component of the action of nitrates in angina (Taylor, 1984), but the effect is offset by an increase in heart rate and inotropic activity (Bennett & Davis, 1985). In addition, tolerance to the antianginal effect of TN appears with time (Parker & Fung, 1984), and so it may be difficult to demonstrate an effect after chronic administration. It has been suggested that constant low plasma levels are more likely to produce tolerance than intermittent peak levels (Parker *et al.*, 1983).

The most probable explanation for the observed lack of efficacy of the 10 cm² patch is that the dose of GTN delivered is inadequate. The plasma concentrations of GTN observed after TN are dose-dependent, but the haemodynamic effects are not (Müller *et al.*, 1982). It has proved difficult to establish a dose-response relationship for TN. In one study, 10 cm² and 20 cm² patches were equally effective (Cerri *et al.*, 1984), whereas in another, no significant effect was observed even with a 40 cm² patch (Crean *et al.*, 1984). Two studies have indicated that a dose-response relationship does exist. In one, exercise tolerance was improved after 20 cm² or more of TN (Dickstein & Knutsen, 1985). In the other, improved exercise duration was observed at 2 and 4 h after 10–90 cm², but effects after 24 h were observed only after 90 cm² (Parker & Fung, 1984). Clearly such a large surface area of patch is likely to be expensive and cosmetically unacceptable. Attempts to increase the dose delivered by increasing the GTN content of the patch may not be successful, as the rate-limiting step for drug absorption is transfer across the stratum corneum of the skin (Abrams, 1984b; Curry *et al.*, 1984).

Our study confirms previous observations that a single 10 cm² (25 mg) patch of TN cannot be shown to be effective in the treatment of angina, but does not exclude the possibility that a larger dose could be so shown. Further work will be required to determine if this requires an increase in patch area, or an increase in nitrate content of the patch applied.

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