A possible explanation for the absence of anti-anginal properties of transdermal nitroglycerin units: an echocardiographic study

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1 The failure of clinical trials to demonstrate any anti-anginal properties of the transdermal nitroglycerin units has resulted in the re-evaluation of one such product, Transiderm-Nitro.

2 Haemodynamic assessment following the application of 10, 20 and 40 cm² units has been made in eight healthy volunteers over a 6 h period. Measurements of heart rate, blood pressure, stroke volume and left ventricular dimension (by 'M' mode echocardiography) were made 2 h after the application of the units.

3 End diastolic dimension fell by 5.2% and stress by 12.6% implying a reduction in myocardial oxygen consumption. However this was offset by an increase in double product of 10.7% and in circumferential fibre shortening of 23.4%.

4 These results imply that the doses used produce venodilatation leading to a reduction in myocardial oxygen consumption. However this is counterbalanced by the reflex induced increase in heart rate and inotropic state. It suggests therefore that much larger doses are required to produce significant anti-anginal effects.

Keywords echocardiography nitroglycerin transdermal application volunteers myocardial oxygen consumption

Introduction

The recent introduction of preparations designed to provide continuous transdermal absorption of glyceryl trinitrate (GTN) offers the possibility of continuous 24 h prophylaxis to angina. However recent trials of one such product 'Transiderm-Nitro' (Transiderm-Nitro, Ciba-Geigy Pharmaceuticals, England) in patients with chronic stable angina using one unit applied to the chest wall failed to produce any statistically significant increase in exercise time. Furthermore our own preliminary studies carried out on normal volunteers using the same dose produced no significant haemodynamic effects, although there was a trend for echocardiographically determined left ventricular dimension to decrease 2 h after appli-

cation. This implied that the doses given in both normal volunteer and patient studies were too low.

The present study was therefore undertaken to ascertain whether increased doses of Transiderm-Nitro could produce a significant haemodynamic effect in a group of normal healthy volunteers.

Methods

Eight normal healthy volunteers were studied (three female, five male, age range 20–40 years) using an incremental double-blind cross over protocol with a 1 week wash out period.

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Conventional 'M' mode echocardiography was used to determine left ventricular dimension. From the basic measurements of end diastolic dimension (EDD) and end systolic dimension (ESD), fractional shortening (FS), peak circumferential fibre shortening (VCF) and wall stress (SSS) have been calculated (Popp *et al.*, 1975; Martin *et al.*, 1979; Falsetti *et al.*, 1970). The 'M' mode echo traces were randomised before digital analysis.

In order to obtain cardiac output and stroke volume ascending aortic blood velocity was measured using a Bach-Simpson Doppler blood velocity meter BVM 202 (Iyawe *et al.*, 1983; Bennett *et al.*, 1984). Blood pressure was obtained using conventional sphygmomanometry with the Korotkoff fourth sound being taken as diastolic pressure. Heart rate was obtained from the ECG recorded simultaneously with the echocardiogram. In order to maximise the haemodynamic response all measurements were taken with the subject in a 30° head up tilt position.

After obtaining a set of baseline measurements, one unit was applied to the chest wall and the measurements repeated after 2 h. This unit was then removed and two new units applied in the same way, measurements were again repeated 2 h after application. This procedure was then carried out with four units. Following a 1 week wash out period, the experiment was repeated with the alternative set of units. All the measurements were taken at the same time of day for both the active and placebo days. Lunch was between the 2 h and 4 h measurement.

Statistical analysis

The data used in the statistical analyses represents the difference between the baseline measurement and each respective dose. Each variable was analysed separately using a repeated measures cross-over technique (Wallenstein & Fisher, 1980). This method allows tests for carryover, period and treatment effects. In the event of a statistically significant treatment effect (i.e. $P \leq 0.05$) a comparison

of the three dosages of Transderm-Nitro was made using a single treatment period repeated measures method (Winer, 1971). In addition Fisher's significant difference technique (O'Neil & Wetherill, 1971) was used for a multiple pairwise comparison of the three doses of Transderm-Nitro.

Results

Table 1 shows the mean and s.d. for each variable at baseline, and the mean differences from the baseline values.

Table 2 shows those variables where a statistically significant treatment effect was demonstrated.

There was a significant increase in HR on active compared to placebo ($P \leq 0.005$) of 10 beats/min from baseline for the 20 cm² and 40 cm² units. There was a significant difference between the 10 cm² and the 20 cm²/40 cm² units ($P \leq 0.05$).

In comparison with placebo, systolic blood pressure fell significantly $P \leq 0.05$, the mean reduction from the baseline value were 4, 2 and 3 mmHg for the 10, 20 and 40 cm² units respectively. There was no significant difference between the effects of the three doses. However, DP had a tendency to increase with the 20 and 40 cm² active doses when compared to placebo, although this trend was not significant.

End diastolic dimension was significantly reduced with active when compared to placebo ($P \leq 0.05$), the mean reduction from baseline was 0.14, 0.36 and 0.34 cm for the 10, 20 and 40 cm² units respectively. However, the differences between the doses were not statistically significant. There was a significant decrease in left ventricular wall stress with the active preparation compared to placebo ($P \leq 0.05$). The mean differences from the baseline values were 3.5, 3.5 and 3.9 kPa/cm for the 10, 20 and 40 cm² unit respectively. The differences between the doses were not statistically significant.

Figure 1 Design of the study

Table 1 Mean baseline values and mean differences from baseline for each dose with the active and placebo treatments (mean (s.d.))

Variable	Base-line	Transiderm-Nitro			Base-line	Placebo		
		10	20	40		10	20	40
Heart rate (beats/min)	71 (11)	-5 (13)	10 (11)	10 (11)	74 (10)	-8 (12)	-2 (10)	-5 (8)
Systolic BP (mmHg)	123 (12)	-4 (10)	-2 (11)	-3 (6)	122 (12)	3 (2)	6 (5)	-2 (5)
Diastolic BP (mmHg)	78 (8)	3 (5)	2 (9)	-1 (5)	77 (8)	0 (7)	2 (6)	1 (4)
Double product (beats min ⁻¹ mmHg ⁻¹)	8672 (1566)	-790 (1759)	1008 (2080)	1206 (1516)	8887 (1276)	-661 (1395)	158 (1401)	-631 (944)
Systemic vascular resistance (dyn s ⁻¹ cm ⁻⁵)	1732 (375)	142 (438)	-124 (195)	-82 (351)	1720 (455)	43 (368)	-110 (339)	3 (387)
End diastolic dimension (cm)	4.71 (0.50)	-0.14 (0.34)	-0.36 (0.36)	-0.34 (0.23)	4.64 (0.48)	0.20 (0.21)	0.05 (0.13)	0.06 (0.23)
End systolic dimension (cm)	3.23 (0.36)	-0.08 (0.27)	-0.31 (0.34)	-0.31 (0.25)	3.20 (0.38)	0.08 (0.24)	-0.02 (0.28)	0.02 (0.28)
Left ventricular wall stress (kPa/cm)	26.89 (4.32)	-3.54 (2.92)	-3.49 (3.83)	-3.91 (3.66)	25.19 (3.99)	0.14 (3.48)	1.38 (2.44)	-1.65 (3.05)
Peak circumferential fibre shortening (circ/s)	2.15 (0.50)	0.05 (0.39)	0.39 (0.52)	0.49 (0.61)	2.22 (0.56)	-0.16 (0.45)	0.19 (0.51)	-0.02 (0.38)
Fractional shortening	0.31 (0.05)	0.00 (0.04)	0.02 (0.04)	0.01 (0.05)	0.30 (0.07)	0.02 (0.03)	0.03 (0.05)	0.03 (0.03)
Cardiac output (l/min)	4.46 (0.95)	-0.21 (0.78)	0.29 (0.85)	0.08 (1.05)	4.54 (1.19)	-0.31 (0.83)	0.30 (0.64)	-0.14 (1.00)
Stroke volume (ml)	64.46 (11.13)	-4.86 (9.18)	-6.88 (8.40)	-8.52 (8.71)	62.88 (13.22)	-0.31 (9.29)	3.72 (8.88)	1.57 (12.04)

The increase in peak circumferential fibre shortening when compared to placebo was statistically significant ($P \leq 0.05$). In addition, the measured treatment effect when using the 20 and 40 cm² active units was significantly greater than that of the 10 cm² active unit ($P \leq 0.05$). However the difference between the two higher doses was not significant.

None of the remaining variables showed any difference between placebo and active, although the reductions in stroke volume and end systolic dimension tended to statistical significance with the active preparation. The reported side effect was 'headache'. Table 3 shows the incidence of 'headache' with respect to increasing dose.

Discussion

The interest in the transdermal application of

GTN is founded on two points, firstly this route avoids the first pass effect of the liver and secondly, the design of the unit is such that a steady delivery rate of GTN is maintained throughout a 24 h period of application. Several drug trials have now been carried out in stable angina groups, and in general these data have failed to show statistical significance in the prolongation of exercise time. Crean *et al.* (1983) have recently carried out a study on stable angina patients examining the response to a 10 cm² Transiderm-Nitro unit using exercise testing and 96 h Holter monitoring in a double-blind cross over protocol. The study was unable to demonstrate any significant difference in objective or subjective signs of ischaemia. Reichet *et al.* (1983) have also been unable to demonstrate any significant changes using exercise testing or 24 h Holter monitoring on a similar group of stable angina patients again using a 10 cm² dose.

Table 2 Probability values for the mean differences between active and placebo and the mean differences between the three active doses

<i>Variable</i>	<i>Difference between T-N and placebo</i>	<i>Difference between three doses of T-N</i>
Heart rate	$P = 0.005$	$P = 0.002$ (10 = 20, 10 = 40 – $P > 0.05$)
Systolic BP	$P = 0.039$	$P = 0.81$
Diastolic BP	$P = 0.47$	—
Double product	$P = 0.12$	—
Systemic vascular resistance	$P = 1.00$	—
End diastolic dimension	$P = 0.004$	$P = 0.090$
End systolic dimension	$P = 0.80$	—
Left ventricular wall stress	$P = 0.036$	$P = 0.93$
Peak circumferential fibre shortening	$P > 0.05$	(10 = 20, 10 = 40 $P > 0.05$)
Fractional shortening	$P = 0.94$	—
Cardiac output	$P = 0.83$	—
Stroke volume	$P = 0.93$	—

Table 3 Reported headaches for the eight volunteers

<i>Treatment</i>	<i>Dose (cm²)</i>			
	<i>Baseline</i>	<i>10</i>	<i>20</i>	<i>40</i>
Transiderm-Nitro	0	1	6	7
Placebo	0	2	2	1

Table 4 The percentage change from baseline for each of the three doses with active and placebo treatments for end diastolic dimension (EDD), circumferential fibre shortening (VCF), stress (SSS) and double product (DP).

	<i>10 cm³</i>		<i>20 cm²</i>		<i>40 cm²</i>	
	<i>Active</i>	<i>Placebo</i>	<i>Active</i>	<i>Placebo</i>	<i>Active</i>	<i>Placebo</i>
EDD	–2.06 (1.10)	4.38 (1.99)	–6.86 (1.11)	1.17 (1.25)	–6.51 (0.71)	1.45 (2.17)
VCF	5.9 (2.23)	1.0 (10.11)	31.9 (11.14)	17.5 (13.11)	33.0 (15.47)	4.4 (9.92)
SSS	–13.1 (1.40)	0.5 (5.15)	–12.5 (1.92)	6.2 (2.34)	–12.4 (2.11)	–5.1 (1.99)
DP	–8.8 (2.91)	–9.5 (6.24)	14.6 (3.47)	3.6 (7.31)	17.4 (3.17)	8.9 (3.74)

Table 5 The calculated MVO_2 ($\text{mlO}_2 \text{ min}^{-1} 100 \text{ g}^{-1}$) for each of the three doses using the formula of Rooke & Feigl (1982): $\text{MVO}_2 = k_1 (\text{SBP} \times \text{HR}) + k_2 (0.8\text{SBP} \times 0.2\text{DBP}) \times \text{HR} \times \text{SV} + k_3$ where $k_1 = \frac{\text{BW}}{4.08 \times 10^{-4}}$, $k_2 = 3.25 \times 10^{-4}$, $k_3 = 1.43$ and BW = body weight (kg), HR = heart rate, SV = stroke volume, SBP = systolic blood pressure, DBP = diastolic blood pressure,

	Active unit	Placebo unit
Control	7.49 (1.56)	7.57 (1.32)
10 cm ²	6.53 (1.15)	6.92 (1.15)
20 cm ²	7.59 (1.28)	7.95 (1.19)
40 cm ²	7.93 (1.51)	7.14 (1.07)

These negative findings may be explained, when consideration is given to the actual dose delivered by the transdermal unit. The 10 cm² unit delivers approximately 4 µg/min. Bayley *et al.* (1984) have shown that such a dose given intravenously produces only mild venodilatation reflected by a significant lowering of the pulmonary capillary wedge pressure in patients with left ventricular failure.

To clarify the situation a dose response study was carried out using three doses of Transiderm-Nitro. On the basis of previous studies carried out within this department (Bennett & Davis, 1984), haemodynamic measurements were carried out 2 h after the application of the Transiderm-Nitro units.

The major effect of an anti-anginal agent is that it should cause a lowering in myocardial oxygen consumption (MVO_2). The factors determining MVO_2 are wall tension, contractility, heart rate and blood pressure (Sonnenblick & Skelton, 1971; Weber & Janicki, 1977; Elzinga, 1983). Therefore we have looked at these factors in this study by observing the changes in wall stress as a measure of wall tension, mean circumferential fibre shortening as an index of contractility and have directly measured heart rate and blood pressure in order to calculate double product.

We have demonstrated in Table 4 the percentage changes in SSS, VCF and DP. The significant fall in SSS for all three doses

confirms the venodilatory effect of the units. With the 10 cm² unit, although there was a fall in DP this was probably due to a diurnal variation and not a response to therapy as it occurred following administration of the placebo unit.

In contrast the DP rose with the 20 and 40 cm² units presumably due to an increase in sympathetic activity confirmed by a similar increase in VCF. These results suggest that although MVO_2 fell as a result of venodilatation any benefit was counterbalanced by the secondary increase in MVO_2 resulting from the increase in DP and VCF. To further substantiate these findings we have calculated MVO_2 using the formula derived by Rooke & Feigl (1982) from a series of dog experiments. They found that the equation (illustrated in Table 5) correlates well with directly measured MVO_2 . Substituting our data into this formula shows that the active units failed to produce any reduction in the calculated MVO_2 .

Hence it appears that the application of transdermal GTN at the doses used in this study undoubtedly produce venodilatation resulting in a reduction in SSS. However the subsequent decrease in stroke volume leads to a reflex increase in sympathetic activity, which in turn leads to a tachycardia and increased inotropic state. It is likely that in the clinical situation Beta blockade would be prescribed and this would probably lead to the attenuation of the reflex sympathetic response. Although the patients in our own preliminary study and those of Crean *et al.* (1983) and Reichek *et al.* (1983), were maintained on β-adrenoceptor blockade therapy probably leading to attenuation of the 2^o reflex response, there was still no significant increase in exercise time. In marked contrast the application of GTN cream to a 15 cm square area produced a mean decrease of 15 mmHg in systolic blood pressure and was associated with a significant increase in exercise time of 150 s (Bennett *et al.*, 1983). Although we were unable to calculate the true dose delivered, the area of application, in excess of 200 cm², suggests a considerably higher rate of delivery.

Hence it is not surprising that the clinical trials carried out with the 10 cm² unit have failed to demonstrate any anti-anginal properties. Our results suggest that any further clinical studies should be carried out using significantly higher doses.

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