Objective relief of vasospasm by glyceryl trinitrate in secondary Raynaud's phenomenon

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Summary: An objective response to topical glyceryl trinitrate was shown by digital plethysmography in a study of 17 patients with Raynaud's phenomenon. Improvement was significant ($P < 0.005$) in those in whom the disease was secondary to an underlying connective tissue disorder. The response suggests that the effect of this drug is mediated locally.

Introduction

Raynaud's phenomenon is a common condition; recent estimates of its prevalence are as high as 5–10% of the population (Olsen & Nielson, 1978). It may occur in isolation (primary) or in association with connective tissue diseases such as systemic sclerosis and systemic lupus erythematosus (SLE) (secondary). In its most severe form, digital ulceration and gangrene may result.

Assessment of treatment for Raynaud's phenomenon has been hampered by natural fluctuations in the severity of symptoms, widespread reliance on subjective indices of therapeutic response and difficulties with classification. Despite trials of a wide range of vasoactive drugs, treatment remains unsatisfactory. In one study of patients with secondary Raynaud's phenomenon (Franks, 1982), subjective clinical assessment suggested topical glyceryl trinitrate (GTN) was a useful adjunct to sympatholytic drugs.

We have investigated the activity of GTN alone in both primary and secondary Raynaud's phenomenon using a single objective endpoint measure to determine outcome.

Patients and methods

We undertook a randomized, double-blind, placebo-controlled study in 17 patients with Raynaud's phenomenon using a protocol submitted to and approved by the Central Birmingham Health District Research Ethical Committee. The patients were recruited from hospital outpatient clinics and each gave their consent

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to participate after the nature and purpose of the trial had been explained.

Ten patients had secondary Raynaud's phenomenon and were classified according to the criteria of the American Rheumatism Association for SLE (Tan *et al.*, 1982) or scleroderma (Subcommittee for Scleroderma Criteria of the ARA, 1980). The associated connective tissue disease was scleroderma in 5 and SLE in 4, one patient had a scleroderma overlap syndrome. The primary or idiopathic group were defined by the presence of symmetrical Raynaud's phenomenon, the absence of clinical evidence of connective tissue disease or gangrene, and a disease duration of greater than 5 years.

Response was assessed using the Nielsen apparatus (Nielsen & Lassen, 1977; Nielsen, 1978). On arrival at clinic, patients were first rested for 30 minutes and then moved to a temperature controlled room (20°C) in which all measurements of finger systolic pressure (FSP) were undertaken. For each assessment of FSP a water filled cuff was placed in fixed position over the middle finger. This was perfused by water at controlled temperature and pressure using the mediamatic apparatus. Distal to the cuff was a mercury in silastic plethysmograph sensitive to pulsation in the digital pulp. For these studies the pulp was emptied and the cuff inflated to 200 mmHg pressure at a temperature of 30°C or 15°C for 5 min. The cuff was then deflated at a controlled rate of 2 mmHg/s until the point was reached when the digital pulp refilled. This end point was taken as the finger systolic pressure. The coefficient of variation for repeated measurements on the same patient at different times with this method was 14%. Using this technique a fall in FSP has been demonstrated in patients with Raynaud's phenomenon after local cooling to 15°C, in excess of that seen in healthy volunteers. We believe that this fall in

FSP is an assessment of local vasospasm induced by cold.

For each patient FSP was measured after the digit was exposed to two different cuff temperatures. Measurements were taken in triplicate, first at 30°C and then at 15°C for each patient before and after treatment with active and placebo ointment. After the initial measurements of FSP had been taken, by random assignment each patient had one hand treated with 5 g of 1% GTN in white soft paraffin and the other hand with white soft paraffin alone. The ointment was applied by a single observer (who was blind to treatment) over the hand from the mid palmar crease to the finger tips. After a fixed time of one and a half hours, measurement of FSP at 30°C and then 15°C was repeated (in triplicate), the observer being blind to treatment. Average values of the triplicate measurements were used for subsequent calculations.

For each hand the FSP (at each temperature studied) before treatment was subtracted from the FSP (at the same temperature) after treatment. In each patient we calculated the change in FSP for both the placebo treated hand and the actively treated hand. The difference between these (change due to active treatment − change due to placebo treatment) is the treatment effect, i.e. the effect attributable to GTN.

Non-parametric statistical analysis was performed using the Mann Whitney test.

Results

The condition was symmetrical in individual patients, thus initial finger systolic pressures at 30°C or 15°C were not significantly different between active and placebo treated hands. Patients with primary or secondary Raynaud's phenomenon did not differ significantly in their initial (pre-treatment) FSPs and were similar in terms of age (primary, median 39 years, range 19–74: secondary, 52 years, range 24–73), disease duration (primary, 9.5 years, range 5–15: secondary, 8 years, range 0.5–20) and disease severity, which was assessed subjectively by a 10 cm horizontal visual analogue scale (primary, 65 mm, range 11–86: secondary, 59 mm, range 3–95).

We could demonstrate no significant changes in FSP following treatment in the actively or placebo treated hands alone (see Table I) in any patient group. The secondary group showed a trend towards improvement in the actively treated hand alone at 30°C and 15°C but numbers were too small to attain statistical significance.

The treatment effect did not demonstrate any difference with treatment in the FSP measured at 30°C. However, after cold stress at 15°C, a significant increase in FSP was evident in the whole group ($P < 0.02$). This derived from those patients with secondary Raynaud's phenomenon (see Figure 1) in which GTN treatment significantly increased FSP at 15°C ($P < 0.005$, point estimate of drug effect 45 mm, 95% confidence interval 9 to 63 mm). All but one showed a positive effect of GTN, the non-responder was a patient with a severe scleroderma overlap syndrome and partial finger loss. She had no demonstrable finger blood flow.

In contrast the primary group response was variable, one patient exhibiting a good response to GTN, though there was no overall change in FSP (point

Table 1 Changes in FSP (mmHg) after treatment for the active and placebo treated hands for the two cuff temperatures studied (30°C and 15°C). These were calculated for each patient as the difference between pre-treatment and post-treatment FSP. The treatment effect is the difference between the change in FSP in the actively treated hand and the change in FSP in the placebo treated hand.

	Change in FSP for actively treated hands Cuff temperature		Change in FSP for Placebo treated hands Cuff temperature		Treatment effect Cuff temperature	
	30°C	*15°C*	*30°C*	*15°C*	*30°C*	*15°C*
All patients $n = 17$	24(− 22 to 71)	16(− 22 to 57)	12(− 74 to 52)	0(− 63 to 56)	5(− 48 to 121)	20*(− 56 to 122)
Primary Raynaud's phenomenon $n = 7$	24(− 22 to 71)	0(− 22 to 57)	16(− 35 to 40)	0(− 32 to 56)	4(− 19 to 55)	0(− 56 to 71)
Secondary Raynaud's phenomenon $n = 10$	22.5(− 13 to 58)	31.5(0 to 59)	4.5(− 75 to 40)	−3.5(− 63 to 22)	7.5(− 48 to 121)	44**(0 to 122)

The median value and range (in parentheses) are shown for all patients, and those with primary or secondary Raynaud's phenomenon at the two different cuff temperatures. *$P < 0.02$, **$P < 0.005$ (Mann Whitney).
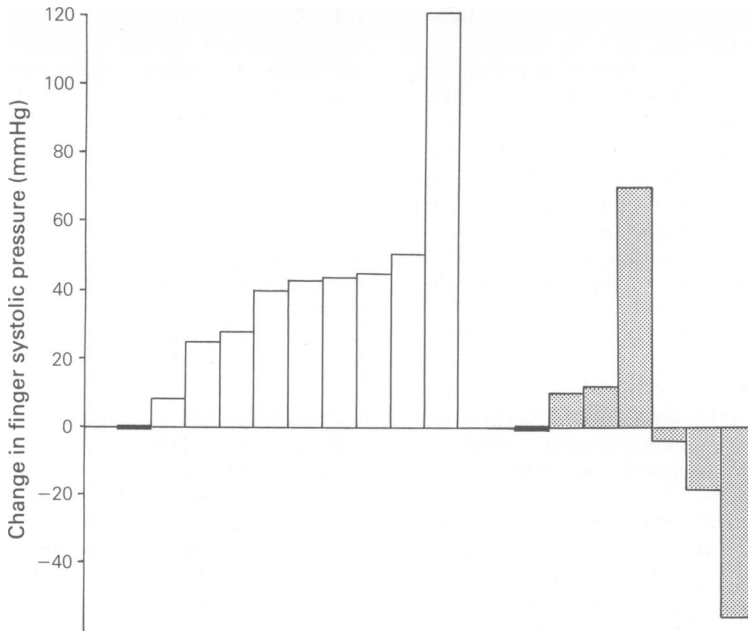
Figure 1   Treatment effect for individual patients – cuff temperature 15°C. (▨) primary; (□) secondary.

estimate 0 mm, 95% confidence interval − 45 to 39 mm).

No relationship was seen between immunological abnormalities and change in FSP. None of the patients with primary Raynaud's phenomenon had soluble nuclear antigens, though 2 had weakly positive antinuclear antibodies on Hep-2 cells.

Four patients experienced headache, which we attribute to systemic absorption of GTN. In 3 of these patients the headache commenced over 2 hours after the drug was removed. No other adverse effects occurred.

Discussion

An earlier report (Franks, 1982) suggested topical GTN may be effective in combination with oral vasodilators. The present study, using objective assessments, shows that it can reduce cold-induced vasospasm when used alone in secondary Raynaud's phenomenon. We could demonstrate no such effect in primary Raynaud's phenomenon, though the pattern of response in this group is of interest as it has been shown (Gerbracht et al., 1985; Porter et al., 1976) that on long term follow-up a proportion of these patients develop connective tissue disease. Whilst two patients with primary Raynaud's phenomenon had weakly positive antinuclear antibodies on Hep-2 cells in the absence of diagnosable connective tissue disease, we

could determine no relationship between the occurrence of autoantibodies and response to GTN. The reason for the difference in response of the primary and secondary group is unclear. A recent study of the calcium antagonist, diltiazem, produced exactly the opposite effect (Kahan et al., 1985). Diltiazem appeared to improve those with primary but not those with secondary Raynaud's phenomenon.

Horhota & Fung (1979) have shown that GTN ointment applied to the abdominal skin surface of rats results in elevated serum levels for at least 4 hours and that 60% of the applied GTN is recoverable from skin surface sections after that time. In a study on human subjects with congestive cardiac failure, Armstrong and colleagues (1980) have shown that despite its short half life of 1.9 minutes GTN is still detectable in the serum of patients half an hour after the ointment was removed from the skin by scraping and washing in alcohol. They have suggested that there may be a local depot in the skin for GTN. The late development of headaches in our patients would add further support to this hypothesis. The mechanism of action of GTN remains unclear even in angina pectoris where it has been extensively studied (Editorial, 1984). There is evidence for a dose related effect on coronary vessels of different sizes (Feldman et al., 1982).

Imhof et al. (1980) have suggested that high doses of GTN produce progressive reductions in peripheral arterial resistance. The asymmetry of response with this agent in our patients suggests that its action is

predominantly local perhaps reflecting a high concentration of GTN in the digital tissues. The need for high tissue concentrations could also explain the lack of effectiveness of systemic GTN (Sovijarvi *et al.*, 1984) in Raynaud's phenomenon.

The long term efficacy of GTN remains to be shown but it clearly has an effect on finger systolic pressure, though the pharmacokinetics of this action require further study. Whether this effect improves nutritional blood flow is unclear but its simplicity and lack of serious side effects makes it a candidate for long-term

studies. It appears that topical GTN offers an acceptable, safe therapy for Raynaud's phenomenon and we are currently assessing long-term efficacy with this and other methods of drug delivery.

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