Clinical and rheological effects of nifedipine in Raynaud's phenomenon

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1 Thirty-four patients with Raynaud's phenomenon, 28 primary and six secondary, were entered into a double-blind placebo controlled, randomized cross-over trial of nifedipine treatment. Nifedipine was given as a 20 mg biphasic release formulation twice daily.

2 Twenty-nine patients completed the study, during which the mean number of attacks was reduced by 25% during nifedipine treatment ($P < 0.001$). Twenty patients scored nifedipine higher than placebo on a five point rating scale ($P < 0.001$).

3 Unwanted effects were experienced by 26 patients during active treatment, resulting in withdrawal from the study in five.

4 Red cell deformability and fibrinogen concentrations were not altered by nifedipine.

Keywords nifedipine Raynaud's phenomenon

Introduction

Raynaud's phenomenon is characterized by reversible vascular spasm of the extremities provoked by stimuli such as emotion or cold (Blunt & Porter, 1981). The treatment of this disorder is unsatisfactory but vasodilator drugs have been used with some benefit. Among these, nifedipine, a slow calcium channel antagonist has been evaluated with some success (Smith & McKendry, 1982; Kahan *et al.*, 1983; Rodeheffer *et al.*, 1983; Creager *et al.*, 1984; Ettinger *et al.*, 1984; Sauza *et al.*, 1984; Nilsson *et al.*, 1984; Corbin *et al.*, 1986). Some of these studies have included only small numbers of patients. In most, the majority of patients had Raynaud's phenomenon secondary to another disorder, unlike those in the current study who mainly had primary Raynaud's phenomenon.

The aetiology of Raynaud's phenomenon is unknown, but there is evidence to suggest that reduced red cell deformability may contribute to the impairment of flow (Lucas *et al.*, 1984). Accumulation of cytoskeletal calcium is known to reduce membrane flexibility (Weed *et al.*,

1969) and antagonists of the inward transmembrane calcium flux might exert a favourable effect on red cell deformability by preventing accumulation of intracellular calcium. We have, therefore, investigated the possibility that nifedipine may improve blood flow in Raynaud's phenomenon by modifying red cell deformability, using methods previously shown to demonstrate rheological activity of nifedipine (Waller *et al.*, 1984a; Francis *et al.*, 1985).

Methods

Patients

Thirty-four patients entered the study which was conducted between November 1984 and May 1985. Raynaud's phenomenon was diagnosed on typical clinical history (Blunt & Porter, 1981) and considered primary after exclusion of other conditions by history, examination and haematological and immunological blood tests.

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Twenty-eight had primary Raynaud's phenomenon and in six it was secondary to scleroderma (4) or rheumatoid arthritis (2). Eight were male and 26 female, with a mean age 45 years (range 14–77 years), and a mean duration of Raynaud's of 14.7 years (range 0.5–48 years). Ten were smokers. Concurrent treatment, which was continued unchanged in 16 patients, consisted of a diuretic (four patients), non-steroidal anti-inflammatory drugs (3), oral contraceptive pill (3), prednisolone (1), azathioprine (1), benzodiazepine (2), digoxin (1), thyroxine (1), chlorpheniramine (1), slow release iron (1) and a homeopathic remedy (1).

The study was approved by the ethical sub-committee of the Southampton and South West Hampshire Health Authority and all patients gave written informed consent.

Study design

Patients were randomized after a 2 week run-in period to receive either 20 mg of a new biphasic release formulation of nifedipine (5 mg fast release, 15 mg slow release) twice daily before food, or matching placebo. Each study period lasted 4 weeks with a 2 week wash-out period between. Mean temperature estimations were obtained for the City of Southampton from the Meteorological Office. This temperature was assumed to be applicable to the 12 patients who came from nearby surrounding areas. Compliance with the tablet regime was assessed by tablet count. At each treatment period 60 tablets were provided. Compliance during active treatment was assessed as good (< 12 tablets returned), moderate (12–34 tablets returned) or poor (> 34 tablets returned).

Measurements

(a) Record diary: Patients were requested to keep a daily record of episodes of Raynaud's phenomenon noting the number of attacks and their severity, graded as mild (1), moderate (2) or severe (3). Other effects which might have been attributed to the tablets were also noted, or elicited by open enquiry.

(b) At the end of each treatment and the wash-out periods, response was assessed on a five point scale. The rating was 1. much better, 2. better, 3. the same, 4. worse, 5. much worse.

(c) At the same time as the rating scale assessment, a 10 cm visual analogue assessment was also completed, graded from 0 (much better) to 10 (much worse).

(d) Blood samples were collected at each visit. Red cell deformability was assessed by filtration

of heparinized whole blood through 5 μ m Hema-fil filters, after removal of leucocytes and platelets with Imugard IG500 wool, as previously described (Francis *et al.*, 1985). Red cell packing rate was also determined using the centrifugation technique described by Sirs (1970), and fibrinogen measured with a commercially available Clauss clotting technique (Immuno Diagnostics).

(e) Plasma was obtained for nifedipine concentration at the end of each treatment period and analysed as previously described (Waller *et al.*, 1984b). Precautions to prevent photo-degradation were observed. Where possible, plasma concentrations were measured 1.5–4 h after the last dose of nifedipine to coincide with expected peak concentration after the biphasic tablet.

Statistical analysis

Results are expressed as mean $\pm$ s.e. mean. Clinical data were analysed using two tailed, non-parametric analysis for cross-over trials (Hills & Armitage, 1979). The method of paired differences for quantitative and ordinal responses was used to assess independently for treatment and order effects during both treatment and wash-out periods. Rheological effects were assessed by Student's *t*-test for paired data.

Results

Five patients (three primary, two secondary) withdrew from the study because of unwanted effects on starting active treatment. One patient reduced the dose of nifedipine to one tablet daily for the last 2 weeks of active treatment because of unwanted effects, and another patient only received 2 weeks of active treatment because personal commitments prevented completion of the study. The latter two patients are included in the analysis. No order effects or treatment-order interactions were found.

Clinical response

Mean ambient temperatures were $6.7^{\circ}\text{C} \pm 0.5$ in the placebo period, $6.9^{\circ}\text{C} \pm 0.6$ during the wash-out period and $6.5^{\circ}\text{C} \pm 0.5$ during the active treatment. The mean frequency of attacks was assessed in 27 of the 29 patients who completed the study; the diary was uninterpretable in the other two. The mean number of attacks per week was reduced from 10.0 ± 1.8 (median 7.0, interquartile range 3.9–13.7) on placebo to 7.5 ± 1.6 (median 6.7, interquartile range

1.4–13.0) on nifedipine ($P < 0.001$) (Figure 1). Three patients were free from attacks during active treatment, and one during the placebo period. In those patients who continued to have attacks during both treatment periods, the mean severity was reduced from 1.8 ± 0.1 to 1.5 ± 0.1 on the 3 point rating scale ($P < 0.001$). Nifedipine was rated higher than placebo by 20 patients (69%) on the five-point scale (Figure 2) and by 23 patients (79%) on the visual analogue scale (VAS) ($P < 0.001$ for both treatment effects). Mean improvement on the visual analogue scale was from 4.9 for placebo to 3.0 for active treatment (Figure 3). The number of attacks and assessment of severity during the wash-out phase did not differ from placebo. Unwanted effects were experienced by 26 patients with nifedipine and five during placebo treatment (Table 1).

Figure 2 Assessment of benefit from placebo and nifedipine using the 5 point rating score.

Figure 1 Mean numbers of attacks of Raynaud's phenomenon during treatment with placebo and nifedipine.

Tablet counts, available for 25 patients who completed the trial, revealed that compliance was good in 23 and moderate in two patients.

The plasma nifedipine concentrations were obtained from 28 of the patients who completed the trial. In 25 patients who had samples taken between 1.5 and 4 h after the last tablet, the concentration ranged from 0 to 123 ng ml^{-1} (mean $48 \pm 7 \text{ ng ml}^{-1}$). Low concentrations of $< 10 \text{ ng ml}^{-1}$ were found in four patients, one of whom had only moderate compliance on tablet count. There was a correlation between the change in VAS responses from placebo to active treatment and plasma nifedipine concentration ($r = 0.455$, $n = 25$, $P < 0.05$).

Laboratory assessment

There were no differences in red cell filtration, red cell packing rate or plasma fibrinogen concentration between active and placebo treatment (Table 2).

Discussion

Nifedipine at a dose of 40 mg day^{-1} resulted in a 25% reduction in the mean number of episodes of Raynaud's phenomenon experienced by the 27 patients with adequate diary assessment. Preference for nifedipine on the visual analogue scale was marginal in three patients and therefore the improvement in 20 on the five-point rating scale is probably a more accurate representation. However, unwanted effects were frequent and often persistent, only seven patients had no problems while receiving active treatment. It is possible that the higher incidence of

Figure 3 Assessment of benefit from placebo and nifedipine on the visual analogue scale.

Table 1 Numbers of patients experiencing individual unwanted effects during the study

	<i>Duration <3 weeks</i>	<i>Symptoms at withdrawal</i>	<i>Present after 4 weeks treatment</i>	<i>Duration unknown</i>
Flushing	14	4	6	2
Headache	11	2	3	1
Oedema	8	3	5	
Parasthesiae	2		1	
Nausea	2	1		
Palpitations	1		1	
Rash	1			
Dysgeusia	1			
Menorrhagia	1			
Cramps	1			
Shaking	2	1		
Dyspnoea	1			
Chest pain	1			
Dry hands	1	1		
<i>(b) During placebo treatment</i>				
Flushing	1		3	
Headache	1			
Oedema			1	
Depression			3	
Dysgeusia			1	
Shaking			1	

Table 2 Rheological measurements during treatment with nifedipine or placebo

	n	Placebo	Nifedipine
Filtration (ml min ⁻¹)	29	3.96 ± 0.08	3.94 ± 0.11
Centrifugation (% min ⁻¹)	24	5.91 ± 0.33	6.39 ± 0.40
Fibrinogen (g l ⁻¹)	28	2.66 ± 0.13	2.70 ± 0.16

side effects on active treatment may have introduced some bias in treatment assessment by the patient. However, the consistency of response with those patients not experiencing unwanted effects, and short duration of the effects in others reduces this possibility. These overall results are consistent with previously reported findings for studies using doses of nifedipine up to 60 mg day⁻¹.

Peak plasma concentrations were greater than 20 ng ml⁻¹ in at least 20 of the patients who completed the study, which corresponds to expected concentrations from previous studies with this preparation (Waller *et al.*, 1984b; unpublished data). The concentrations were similar to those giving a therapeutic response in patients with angina (Stern *et al.*, 1984). There was some evidence that response was better in those patients with higher plasma concentrations, suggesting that individual dose titration may enhance the response. Persistent adverse effects were reported by five patients and occurred in association with a wide range of plasma nifedipine concentrations (10–91 ng ml⁻¹).

The mechanism by which nifedipine exerts its effects remains uncertain. Objective evidence for an effect on digital vascular reactivity has been demonstrated by some investigators (Creager *et al.*, 1984; Nilsson *et al.*, 1984) but not by others (Smith & McKendry, 1982; Rodeheffer *et al.*, 1983; Corbin *et al.*, 1986). Among the

postulated pathophysiological features of Raynaud's phenomenon is an increased microvascular blood viscosity due to increased fibrinogen, platelet adhesion or decreased red cell deformability (Coffman & Cohen, 1971; Lucas *et al.*, 1984; Dintenfass, 1977).

There were no differences in red cell deformability while on nifedipine compared to placebo. Previous work has shown that while calcium antagonists can improve the deformability of abnormal red cells (Francis *et al.*, 1985; Sowemino-Coker *et al.*, 1985a) they have no effect on normal cells (Perret *et al.*, 1984; Sowemino-Coker *et al.*, 1985b; Francis *et al.*, 1985). This suggests that impaired red cell deformability is not an important pathogenic mechanism in primary Raynaud's phenomenon.

We, therefore, conclude that nifedipine may be effective in relieving symptoms in some patients with Raynaud's phenomenon, but that unwanted effects are frequent and limit its usefulness. The results are sufficiently encouraging to warrant study of newer calcium channel antagonist drugs with potentially fewer unwanted effects. Further studies to determine their mechanism of action may give insight into the pathophysiology of this condition.

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