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NIFEDIPINE AS A THERAPEUTIC MODALITY FOR RAYNAUD'S PHENOMENON

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Eight patients with Raynaud's phenomenon were entered into a double-blind crossover study of nifedipine versus placebo, with 7 patients undergoing finger plethysmography before and after sublingual nifedipine administration. While receiving nifedipine, all patients reported decreased frequency and severity of attacks, and 4 of 5 had digital ulcer healing. Total finger blood flow increased in 5 of 6 patients after treatment with sublingual nifedipine. This preliminary study indicates that nifedipine may be a useful agent for treatment of digital vasospasm.

Raynaud's phenomenon is a disorder characterized by digital vasospasm, with sequential phases of digital pallor, cyanosis, and erythema. Attacks are generally precipitated by exposure to cold or emotional stimuli and remit spontaneously. However, in some people these attacks may be functionally incapacitating or result in digital ulcers or gangrene. To date, therapy for this disorder has been disappointing and is often limited by untoward side effects (1–3).

Nifedipine is one of the calcium channel blocking agents that can induce vasodilatation, and it is effective in treating angina pectoris due to coronary artery spasm. It interferes with vascular smooth muscle contraction by antagonizing calcium influx via the slow inward channels (4–6). Our study was based on the presumption that this agent could decrease or prevent episodes of Raynaud's phenomenon and increase finger blood flow by inhibiting digital vascular smooth muscle contraction. Additionally, an uncontrolled study reported that nifedipine increased the time of onset of vasospasm induced by cold water immersion, and in therapeutic use it decreased the number of attacks of Raynaud's phenomenon (7,8).

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PATIENTS AND METHODS

Patients. A total of 8 patients were enrolled in the study from March 24, 1982 through May 26, 1982. The group (Table 1) consisted of 6 females and 2 males with an age range of 30–61 years and duration of Raynaud's phenomenon from 3–28 years. Raynaud's phenomenon was diagnosed by characteristic episodes of digital color changes on exposure to cold and/or emotional stimuli. Three patients had primary Raynaud's disease and 5 had Raynaud's phenomenon associated with a collagen vascular disorder (2 progressive systemic sclerosis [PSS], 1 CREST [calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, telangiectasia], 1 systemic lupus erythematosus [SLE], 1 rheumatoid arthritis [RA]); attacks occurred daily in 7 of 8 patients and several times per week in 1. Five patients had positive antinuclear antibodies (titer from 1:32 to 1:4,096); circulating immune complexes were slightly elevated in 2; C4 was decreased in 4 of 7 patients evaluated (0.12–0.14, normal 0.15–0.54); and rheumatoid factor positive in 1 of 8 (patient 3). Only 1 patient (patient 8) was taking a medication that might influence Raynaud's (propranolol), and none of the patients smoked cigarettes.

The study was divided into 2 parts: a clinical double-blind crossover trial with oral nifedipine (Pfizer Pharmaceuticals, Inc.) and placebo, and a fingertip blood flow study with sublingual nifedipine challenge.

All patients underwent a complete history and physical examination prior to entering the study. Baseline laboratory evaluations (hemograms, blood urea nitrogen [BUN], creatinine, electrolytes, liver function tests, and urinalysis) were obtained upon entry and at crossover. Additionally,

Table 1. Characteristics of patients with Raynaud's phenomenon/disease*

Patient	Age/ sex	Type of Raynaud's/ underlying disorder	Duration Raynaud's (years)	Frequency of attacks	Area of involvement	Precipitating cause(s)	Ulcers
1	61/M	2°/CREST	5	D	F + T	C/E	+
2	35/F	2°/RA	15	D	F + T	C/E	–
3	31/F	2°SLE	4	D	F + T	C/E	+
4	39/F	1°	28	W	F + T	C/E	–
5	55/M	2°/PSS	10	D	F	C	+
6	30/F	1°	10	D	F + T	C/E	–
7	60/F	2°/PSS	4	D	F + T	C/E	+
8	52/F	1°	3	D	F + T	C/E	+

* CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; D = daily; F = fingers; T = toes; C/E = cold- and emotion-induced attacks; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; W = weekly; PSS = progressive systemic sclerosis; C = cold-induced attacks only.

patients had an electrocardiogram and chest roentgenogram if not done within the preceding 6 months. Immunologic parameters were obtained at entry, as noted earlier. All patients kept a daily diary to record the frequency and severity of vasospastic attacks.

For the clinical trial, patients were randomly assigned to receive either nifedipine or placebo for the first period and were switched to the alternate agent for an equal time, after a 1-day "washout" phase. The study period for each agent was a minimum of 3 weeks, with patients receiving nifedipine and placebo for an equal time. The initial dosage was 1 tablet (10 mg nifedipine or 1 placebo tablet) 4 times daily, increased to 2 tablets 4 times daily if no significant improvement or side effects had occurred.

Fingertip blood flow studies were performed in 7 of 8 patients at a time when they were taking no vasoactive medication. Measurements were obtained by venous occlusion air plethysmography as previously described (2). Baseline measurements of finger blood flow were made in a temperature controlled room cooled to 20°C (2). Each patient then received 10 mg of sublingual nifedipine, and flow studies were repeated. Blood pressure measurements were obtained before and after drug administration. The flow measurements obtained during peak hypotensive effect were averaged and compared with control values. Fingertip vascular resistance was calculated as the ratio of mean blood pressure to fingertip blood flow.

The efficacy of the study drug (nifedipine or placebo) for Raynaud's phenomenon/disease was evaluated at each visit as follows. Each study subject was questioned about the change in frequency of attacks, change in severity of attacks, areas of involvement, precipitating events for attacks, change in functional limitations, overall subjective change (measured on a visual analog scale ranging from worse to better with a neutral point midway for no change), and side effects. Patients were examined at each visit with evaluation for pulse, blood pressure, and ulcers. Statistical analysis was performed using a 2-tailed exact test based on binomial probabilities among discordant pairs.

RESULTS

Clinical response. Results are summarized in Table 2. All patients subjectively noted both decreased frequency and severity of attacks while receiving nifedipine, compared with placebo. This was confirmed by reviewing their daily diaries and visual analog scales. Seventy-five percent of patients reported fewer functional limitations while receiving the drug versus 13% while receiving placebo. All 8 patients had a history of cold-induced attacks, with 88%

Table 2. Positive response to therapy with placebo and nifedipine

Parameter	Placebo (%)	Nifedepine (%)	P*
Frequency of attacks	2/8 (25)	8/8 (100)	<0.05
Severity of attacks	2/8† (25)	8/8 (100)	<0.05
Decreased functional limitations	1/8 (13)	6/8 (75)	0.11
Subjective (analog scale)	2/8† (25)	8/8 (100)	<0.05
Cold-induced attacks	1/8 (13)	7/8 (88)	0.07
Emotion-induced attacks	0/7 (0)	5/7 (71)	0.06
Ulcer healing	0/5‡	4/5 (80)	0.13
Blood pressure decrease	5/8 (63)	6/8 (75)	NS
Pulse increase§	2/6 (33)	3/6 (50)	NS
Flow studies		5/6 (83)	
Side effects¶	4/8 (50)	4/8 (50)	0.50

* Statistical analysis was performed using a 2-tailed exact test based on binomial probabilities among discordant pairs. NS = not significant.

† One of these 2 patients noted a greater improvement with nifedipine than with placebo.

‡ Five of 5 patients developed ulcers while receiving placebo.

§ Insufficient data in 2 patients.

¶ Study was discontinued in 1 patient while receiving placebo because of vomiting. No patients required discontinuance while receiving drug. One patient had an increase in serum creatinine with drug at time of crossover.

Table 3. Side effects reported with placebo and nifedipine*

Side effect	Placebo	Nifedipine
Headaches		1
Dizziness		1
Facial burning/flushing		1
Nausea	1	
Vomiting	2	
Heartburn		1
Constipation		1
Leg edema		2
Ulcers more severe	1	

* Several patients had more than 1 side effect with study agent. A total of 4 patients complained of side effects while receiving each drug. Numbers shown represent number of patients reporting side effect.

experiencing improvement with nifedipine versus 13% having improvement with placebo ($P = 0.07$). Seven of the patients also had experienced emotion-induced attacks; 71% reported improvement with nifedipine but none responded to placebo ($P = 0.06$). All patients had fewer attacks involving their fingers while receiving nifedipine, with attacks involving the toes decreasing in 6 of 7 patients.

Five patients had ulcers believed to be secondary to their Raynaud's. Eighty percent (4 of 5) had healing of ulcers when receiving nifedipine, while all 5 *developed* additional ulcers while receiving placebo. The 1 patient who did not heal with nifedipine had severe PSS (patient 5). Six of 8 patients receiving nifedipine and 5 of 8 patients taking placebo had decreases in blood pressure, none of which caused clinically significant hypotension. Three of 6 patients taking nifedipine and 2 of 6 patients taking placebo were also noted to have increased pulse rates, again without any clinical significance.

The study was discontinued and the code broken in 1 patient (patient 8) who developed vomiting while in the study and was found to be taking placebo at that time. She had already completed the study period with nifedipine and did not report any side effects while receiving this agent. The vomiting was believed to be due to a viral syndrome. Another patient (patient 5 with PSS) had an increase in serum creatinine while taking nifedipine. He was not hypertensive during or after the study period and was entered into the crossover phase. One week after crossover to placebo his creatinine decreased to his baseline of 2.0; at the end of placebo therapy it had again increased to 3.0. Followup 1 week after study revealed a return to baseline serum creatinine of 2.1. During this fluctuation of his serum creatinine, his BUN remained stable. An equal number of patients (4 of 8) reported side effects while receiving placebo as those reporting side effects while taking nifedipine. The side effects are summarized in Table 3.

Finger hemodynamic measurements (Figure 1). Seven of the 8 patients underwent fingertip plethysmography. One of these studies was technically inadequate for interpretation. Fingertip blood flow averaged 8.0 ml/100 ml tissue/minute before nifedipine and 7.1 ml/100 ml tissue/minute after nifedipine, but only 1 patient had a decrease in blood flow. This patient was not as vasoconstricted as the others. Indeed, her blood flow prior to treatment was 10-fold greater than the others and was comparable with normal values (9). Fingertip vascular resistance was 43 units prior to and 25 units after nifedipine, consistent with the vasodilatory response observed in 5 of the 6 subjects. Both patients with primary Raynaud's disease who were tested had an improvement in fingertip blood flow following nifedipine. The patient with a decrease in blood flow had Raynaud's phenomenon secondary to scleroderma. Although there was an improvement in fingertip blood flow in most patients following nifedipine administration, none had blood flows fully corrected to previously established normal values. (Values averaging 33 ml/100 ml tissue/minute have been reported in normal subjects studied in a room cooled to 20°C.)

The onset of the blood pressure response varied from 3 to 10 minutes, with the peak effect occurring 8 to 15 minutes after nifedipine administration. The mean blood pressure decreased in 5 of 6 patients following nifedipine, from an average of 95 to 88 mmHg. The fall in blood pressure in each patient did

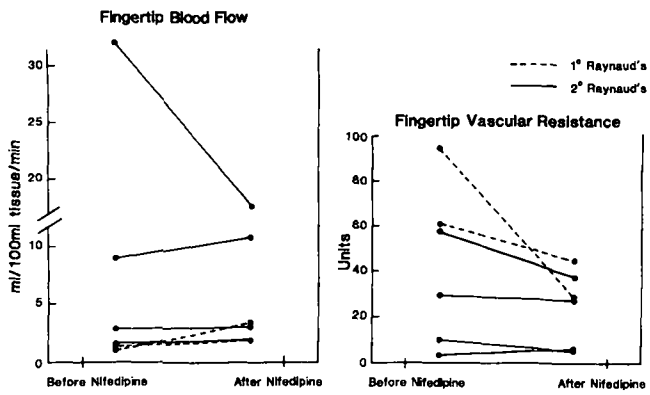

Figure 1. Results of fingertip plethysmography performed on 7 of 8 patients with Raynaud's phenomenon/disease, before and after sublingual nifedipine challenge.

not correlate with the improvement in fingertip blood flow.

DISCUSSION

The results of our preliminary study of the use of nifedipine as a therapeutic agent in Raynaud's are encouraging. While the number of patients enrolled in the study group is small, the clinical response, ulcer healing, and apparent increase in fingertip blood flow after nifedipine administration are promising findings.

In our study, patients were able to tolerate this drug equally as well as placebo (50% reported "side effects" with each agent), and in no case was nifedipine discontinued because of intolerance. One patient had an increase in his serum creatinine while receiving nifedipine; however, the fluctuations of his serum creatinine make interpretation difficult. The etiology of his renal dysfunction may be related to the drug, but since renal function also deteriorated while he was taking placebo, the issue remains unclear and further studies in patients with PSS are necessary.

Patients with Raynaud's phenomenon/disease are often incapacitated in winter months, and they may have severe functional limitation throughout the year. To date there have been no agents or procedures that have been successful in a significant proportion of patients. Further, the majority of present therapeutic approaches have untoward side effects. Although this is a preliminary trial, we believe nifedipine may be a well tolerated, effective agent for digital vasospasm. Additional studies are needed to define the role of nifedipine in the long-term treatment of serious Raynaud's phenomenon.

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