Treatment of Raynaud’s phenomenon with the selective serotonin reuptake inhibitor fluoxetine.

by Drs. B. Coleiro, S. E. Marshall*, C. P. Denton, K. Howell, A. Blann**, K. I. Welsh* and C. M. Black

Centre for Rheumatology (Royal Free Campus), Royal Free and University College School of Medicine, Rowland Hill Street, London, *Oxford Transplant Centre, Churchill Hospital, Oxford and **Haemostasis, Thrombosis and Vascular Biology Unit, City Hospital, University Department of Medicine, Birmingham, UK

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Correspondence to: C. M. Black, Centre for Rheumatology (Royal Free Campus), Royal Free and University College School of Medicine, Rowland Hill Street, London NW3 2PF, UK.

Abstract
Objective. To compare fluoxetine, a selective serotonin reuptake inhibitor, with nifedipine as treatment for primary or secondary Raynaud's phenomenon.

Methods. Twenty-six patients with primary and 27 patients with secondary Raynaud's phenomenon were assigned randomly to receive 6 weeks of treatment with fluoxetine (20 mg daily) or nifedipine (40 mg daily). Following a 2-week washout period, each group was crossed over to the other treatment arm. The primary outcome variable was the frequency of attacks of Raynaud's phenomenon. Self-reported attack severity, thermographic recovery from cold challenge and plasma levels of von Willebrand factor and soluble P-selectin were also measured.

Results. There was a reduction in attack frequency and severity of Raynaud's phenomenon in patients treated with either fluoxetine or nifedipine, but the effect was statistically significant only in the fluoxetine-treated group ($P = 0.0002$ for attack severity and $P = 0.003$ for attack frequency). Subgroup analysis showed that the greatest response was seen in females and in patients with primary Raynaud's phenomenon. A significant improvement in the thermographic response to cold challenge was also seen in female patients with primary Raynaud's phenomenon treated with fluoxetine but not in those treated with nifedipine. There was no significant treatment effect on von Willebrand factor or soluble P-selectin. No significant adverse effects occurred in the fluoxetine-treated group.

Conclusion. This pilot study confirms the tolerability of fluoxetine and suggests that it would be effective as a novel treatment for Raynaud's phenomenon. Larger and placebo-controlled trials are warranted to assess fluoxetine's therapeutic potential further in this vasospastic condition.

KEY WORDS: Raynaud's phenomenon, Scleroderma, Fluoxetine, Nifedipine, Serotonin reuptake inhibitor.

Raynaud's phenomenon is characterized by episodic vasospasm of the extremities precipitated by cold or emotional stress. It was first described by Maurice Raynaud over 100 years ago [1], and may occur as a primary phenomenon or may be secondary to other disorders, such as systemic sclerosis. It is not uncommon, affecting up to 10% of the adult population, and has a female preponderance [2]. The severity of Raynaud's phenomenon varies from mild infrequent episodes to more severe daily attacks that interfere with everyday activities and may result in fingertip ulceration and even gangrene. Treatment may be offered in these more severe cases, usually in the form of a vasodilator drug. Although a variety of

vasodilators are available, none is universally effective and the response to treatment is often idiosyncratic. Moreover, effective vasodilators such as nifedipine may be associated with severe, intolerable side-effects [3]. Hence, different classes of drugs have been assessed for use in the treatment of Raynaud's phenomenon in order to broaden the therapeutic range available, thus increasing the chance of finding a drug that is suitable for the patient in terms of both efficacy and tolerability. The most widely used agents are vasodilators, including a number of different calcium-channel antagonists and a-adrenergic blockers, such as prazosin. Most of these drugs have dose-dependent side-effects, such as headache, ankle edema and postural hypotension. It seems likely that the most effective drugs will be those which directly target key mediators, and a search for novel agents has led to studies of angiotension receptor antagonists [4] and of the potent synthetic antioxidant probucol [5]. Both of these drugs were apparently superior to nifedipine in controlled clinical trials.

The pathogenesis of the altered vascular tone that underlies Raynaud's phenomenon is incompletely understood and it is possible that several mechanisms are responsible. An increasing body of evidence suggests that serotonin may be involved. Serotonin is a selective vasoconstrictor in vivo: infusion of serotonin into the human brachial artery resulted in the characteristic sequential color changes of Raynaud's phenomenon [6, 7]. Also, ketanserin, a serotonin antagonist that acts by blocking serotonin 2 receptors, has been used successfully in the treatment of Raynaud's phenomenon, improving digital arterial flow at all temperatures and reproducibly relieving cold-induced vasoconstriction [8]. It should be noted that a subsequent placebo controlled trial was not positive [9]. There have been anecdotal reports suggesting that fluoxetine is beneficial in Raynaud's phenomenon [10, 11].

Alteration in endothelial function and platelet activation may be responsible for some of the clinical aspects of Raynaud's phenomenon and scleroderma [12]; increased levels of plasma markers of endothelial function and platelet activation in patients with connective tissues diseases are evidence of this involvement [13]. Indeed, high levels of von Willebrand factor, indicating severe endothelial damage, are a poor prognostic indicator in systemic sclerosis [14]. Furthermore, adenosine nucleotides and serotonin (possibly arising from platelets) stimulate the release of von Willebrand factor from endothelial cells in vitro [15].

We hypothesized that treatment of patients with primary or secondary Raynaud's phenomenon with a selective serotonin reuptake inhibitor (SSRI) would lead to a reduction in symptoms, and the present study was conducted to assess the therapeutic potential of fluoxetine in a much larger cohort of well-characterized patients with primary or secondary Raynaud's phenomenon. To assess its possible future use in clinical practice, we compared its effects with those of nifedipine, currently the most widely used vasoactive drug for Raynaud's phenomenon, and we specifically compared the responses to these two agents in order to investigate our clinical suspicion that individual patients demonstrate significantly different responses to a variety of therapeutic interventions. Subgroup analysis was used to identify particular subgroups of patients who were more likely to derive benefit from this alternative therapeutic agent.

Methods

Study design

This was a prospective, randomized cross-over study conducted over a period of 16 weeks during one winter. The study was approved by the Royal Free Hospital Ethical Practices Committee. Following recruitment and informed consent, patients discontinued any vasodilator drugs and were advised to start keeping a symptom diary of the frequency and severity of their Raynaud's attacks. After this 2-week washout period, thermography and nailfold capillaroscopy were performed and blood samples taken. Patients were randomized to receive either fluoxetine 20 mg daily or nifedipine LA 40 mg daily for 6 weeks, after which assessments were repeated. After a 2-week washout period, patients crossed over to receive 6 weeks of treatment with the other drug. This was followed by further blood sampling and thermographic assessment.

Patients

Patients were eligible if they were experiencing at least six attacks of Raynaud's phenomenon per week and were aged between 18 and 75 yr. Significant cardiorespiratory and renal disease or epilepsy or any medical condition contraindicating the use of nifedipine or fluoxetine and the concurrent use of calcium channel blockers or SSRIs for other indications were also exclusion criteria. Patients were enrolled consecutively into the study according to these criteria, and comprised a cohort of individuals (mostly living within Greater London) with severe symptomatic Raynaud's phenomenon and willing to participate. Fifty-three patients were recruited into the study, and their characteristics are shown in Table 1. Primary Raynaud's phenomenon was identified by the absence of definite nailfold capillaroscopic abnormalities and negative antinuclear autoantibody reactivity by immunofluorescence on Hep2 substrate using serum diluted 1 : 100 [16].

TABLE 1. Patient characteristics

	Primary Raynaud's phenomenon	Secondary Raynaud's phenomenon[a]	Total
Sex			
Male	6	5	11
Female	20	22	42
Total	26	27	53
Mean age (range) (yr)			
Male	56.6 (44–74)	50.8 (32–67)	
Female	49.2 (29–75)	55.6 (38–70)	

[a]The patients with secondary Raynaud's phenomenon comprised the following: limited cutaneous scleroderma (SSc), 19 patients; diffuse cutaneous SSc, 5 patients; SSc/rheumatoid arthritis overlap syndrome, 2 patients; SSc/myositis overlap syndrome, 1 patient.

Severity and frequency of attacks

Patients were asked to record, on one particular preselected day of every week, the number of attacks of Raynaud's phenomenon occurring that day and to score the average severity of attack using a visual analogue scale on which 0 represented no attacks and 10 the most severe attack ever experienced.

Thermography

Thermography studies were performed before the start of the trial and at the completion of each treatment arm. An infrared thermal imaging camera (Starlight; Insight Vision Systems, Malvern, UK) was used to measure the skin temperature of the hands. All participants were asked to avoid alcohol for 24 h before the study and hot caffeinated drinks and hot meals on the day of the test. During the test, the patients sat comfortably in a temperature-controlled room (23 f 1°C) for 15 min

TABLE 2. Baseline clinical variables in different subgroups of patients

	Severity of attacks (VAS, 0–10) [mean (SEM)]	Number of attacks per day [mean (SEM)]
Primary Raynaud's phenomenon	5.1 (0.45)	2.8 (0.37)
Secondary Raynaud's phenomenon	4.7 (0.39)	3.2 (0.3)
P	0.52	0.41
Males	4.4 (0.58)	2.41 (0.53)
Females	5.04 (0.34)	3.25 (0.25)
P	0.36	0.31
Before starting treatment with fluoxetine	4.35 (0.39)	2.98 (0.31)
Before starting treatment with nifedipine	3.82 (0.36)	2.72 (0.26)
P	0.31	0.53

VAS, visual analogue scale.

before the measurements commenced. A baseline thermal image was obtained, after which the hands were immersed in water at 15°C for 1 min. Gloves were worn for the cold challenge to avoid problems of evaporative cooling, but were removed for re-warming and imaging. Thermal images were recorded immediately after the cold challenge and 10 min later. Re-warming was assessed using the Thermosoft program (EIC, USA), averaging the temperatures of all fingers at baseline and after recovery.

Vascular markers

Venous blood was obtained after non-traumatic venepuncture into 0.11 M sodium citrate. Citrated plasma was withdrawn after centrifugation for 20 min at 1000 g and 4°C and was stored at -70°C until assayed. Von Willebrand factor was measured by an established enzyme-linked immunosorbent assay (ELISA) technique using commercial antisera from Dako (Ely, UK) and reference von Willebrand factor from NIBSC (Potters Bar, UK). Soluble P-selectin was measured by ELISA using commercial reagents (R&D Systems, Abingdon, UK). The intea-assay coefficient of variation (CV) of these ELLSAs was < 5% and the inter-assay CV <10%.

Statistical analysis

Pre- and post-treatment values of clinical variables (severity and frequency of Raynaud's attacks) and serological tests were analysed by paired Student's t-test.

Baseline clinical variables

Table 2 shows the baseline clinical variables in different subgroups before the start of treatment. Although differences existed between these subgroups, they were not statistically significant and were unlikely to account for differences in the treatment response.

Results

Clinical variables

Analysis of the symptom diaries showed that both fluoxetine and nifedipine produced a reduction in the severity and frequency of attacks of Raynaud's phenomenon (Figs 1 and 2 respectively). The reduction in attack severity was statistically significant with fluoxetine (P = 0.0002) but not with nifedipine (P = 0.14). Likewise, it was only fluoxetine that produced a statistically significant reduction in attack frequency (P = 0.003 for fluoxetine compared with P = 0.22 for nifedipine).

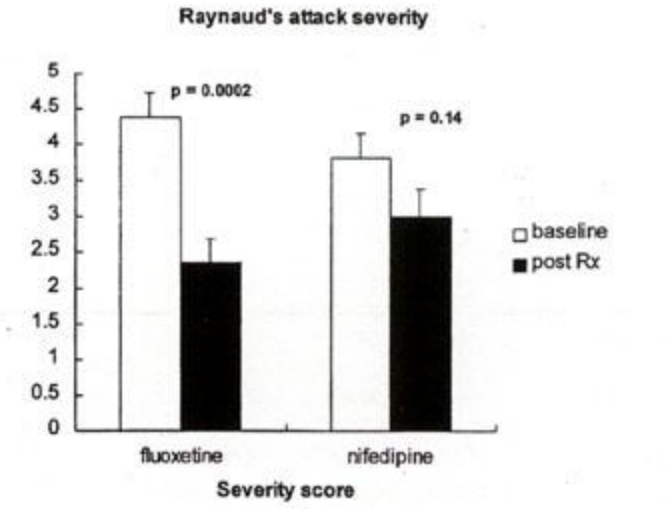

FIG. 1. Improvement in severity of symptoms of Raynaud's phenomenon after treatment. Mean (+SEM) attack severity (scored 0–10 on a self-reported visual analogue scale) is shown at start of treatment and after completion of fluoxetine or nifedipine therapy. The improvement was significant for fluoxetine ($P = 0.0002$) but not for nifedipine ($P = 0.14$).

Subgroup analysis compared the response to treatment between males and females and between patients with primary and secondary Raynaud's phenomenon. The results showed that fluoxetine induced a reduction in attack severity and frequency in both males and females, but the effect was statistically significant only in females (P < 0.0002 for attack severity and P = 0.0004 for attack frequency). Nifedipine also induced a reduction in attack severity and frequency in both males and females but none of these results were statistically significant. Fluoxetine also produced a statistically significant reduction in attack severity both in patients with primary Raynaud's phenomenon and in patients with secondary Raynaud's phenomenon (P = 0.009 and 0.01 respectively). Although the former responded slightly better, the difference was not statistically significant (P = 0.65 for attack severity and P = 0.78 for attack frequency). Fluoxetine-induced reduction in attack frequency was significant only in patients with primary Raynaud's phenomenon (P = 0.003). Nifedipine also resulted in a reduction in attack severity and frequency in both primary and secondary Raynaud's phenomenon groups, but the reductions did not reach statistical significance.

Infrared thermography

More objective evidence of the severity of Raynaud's phenomenon and the response to treatment was obtained from thermographic assessment of the patients at the start of the trial and after each treatment arm. Baseline thermographic data for this series of patients as a whole and for different subgroups are presented in Table 3 together with the percentage increase in hand temperature after a cold challenge. Baseline hand temperature was similar for males and females, and in primary compared with secondary Raynaud's phenomenon. The degree of re-warming after a cold challenge was greater in males compared with females but this difference was not statistically significant (P = 0.16). Patients with primary Raynaud's phenomenon also showed a slightly better response to the cold challenge, but again the effect was not statistically significant. Neither fluoxetine nor nifedipine produced any particular change in the baseline hand temperature of these patients (P = 0.25 and 0.37 respectively).

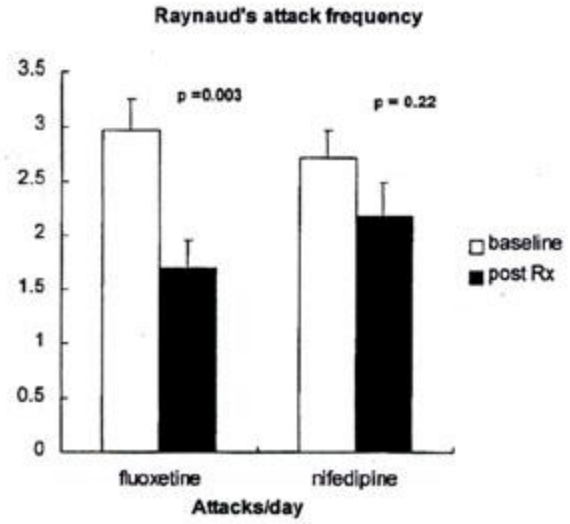

FIG. 2. Reduction in frequency of attacks of Raynaud's phenomenon after treatment. Mean (+SEM) Raynaud's attack frequency (attacks/day) is shown at the start of treatment and after completion of fluoxetine or nifedipine therapy. The reduction in frequency was significant for fluoxetine ($P = 0.003$) but not for nifedipine ($P = 0.22$).

The degree of re-warming after cold challenge was assessed by measuring the increase in hand temperature from immediately after the cold water immersion to 10 min later, and this value was expressed as a percentage of the hand temperature difference immediately before and after the cold challenge. Overall, there was a greater extent of re-warming after a cold challenge after treatment with fluoxetine or nifedipine when compared with the pretrial value. Although the temperature rise was greater with fluoxetine than with nifedipine, neither increase was statistically significant (P = 0.11 and 0.63 respectively). However, subgroup analysis showed that the extent of re-warming was significantly greater after treatment with fluoxetine in females (P = 0.05) but not in males. This corresponds with the significant reduction in the severity and frequency of attacks of Raynaud's phenomenon, as assessed by the symptom diaries, that occurred in the fluoxetine-treated females but not in the males. Neither sex showed a significant improvement in re-warming after treatment with nifedipine.

Table 3. Thermographic assessment of rewarming after the cold challenge

	Average rewarming before trial (% of baseline)	Average rewarming after fluoxetine	P	Average rewarming after nifedipine	P
Whole group	32.4 (4.8)	45.0 (6.3)	0.11	35.9 (5.3)	0.63
Males	45.0 (12.7)	46.6 (17.5)	0.94	44.2 (13.6)	0.97
Females	29.0 (4.9)	44.6 (6.55)	0.05	33.4 (5.7)	0.54
Primary RP	33.4 (7.5)	58.8 (8.7)	0.03	43.1 (8.5)	0.4
Secondary RP	31.6 (6.4)	31.2 (8.2)	0.97	27.5 (5.5)	0.63

RP, Raynaud's phenomenon.

Further subgroup analysis showed that patients with primary Raynaud's phenomenon demonstrated an improvement in re-warming after treatment with either fluoxetine or nifedipine, but this effect was statistically significant only in the fluoxetine-treated patients. Patients with secondary Raynaud's phenomenon did not show any improvement in re-warming with either treatment. This corresponds with the reduction in both attack severity and frequency recorded in the symptom diaries, which was statistically significant in the fluoxetine-treated group with primary Raynaud's phenomenon but not in the fluoxetine treated group with secondary Raynaud's phenomenon.

Vascular markers

Despite changes in symptom or thermographic responses, there was no significant difference in the level of soluble P-selection or von Willebrand factor after treatment with fluoxetine. Thus, for P-selectin the mean (SEM) levels were 127.1 (3.1) at baseline and 125 (4.6) after treatment. For von Willebrand factor, the level was 88.2 (4.0) at baseline and rose to 100.2 (8.6) after the fluoxetine treatment period. No significant changes occurred with nifedipine therapy (data not shown).

Adverse events

Table 4. Frequency of adverse effects

	Fluoxetine No. of patients (%)	Nifedipine No. of patients (%)
Severe side-effects[a]	4 (8.2)	9 (17.6)
Moderate side-effects[b]	5 (10.2)	7 (13.7)
Mild side-effects	22 (44.9)	19 (37.3)

[a]Headaches, nausea, palpitations, apathy, lethargy.
[b]Facial flushing, lower limb swelling.

Although both treatment arms were well tolerated, side-effects were commoner with nifedipine, which led to a higher rate of withdrawal from the trial for this drug than for fluoxetine. Table 4 shows the number and percentage of patients who developed side-effects, which were classed as severe when they resulted in withdrawal from the trial, moderate when they necessitated a dose reduction and mild when they were reported but required no dose adjustment, implying that they were tolerable or transient. The commonest side-effects of nifedipine that led to withdrawal from the trial were severe headaches, nausea and palpitations. Other side effects included facial flushes and swelling of the lower limbs. In the case of fluoxetine, it was apathy, lethargy and impaired concentration that most often led to discontinuation of treatment.

Discussion

Our pilot study assessed the clinical efficacy and tolerability of fluoxetine in a larger number of patients with primary and secondary Raynaud's phenomenon than has been

described in the literature before, and compared its effect with that of nifedipine, a calcium channel blocker that is a well-established treatment for this disorder [17-20]. The results suggest that fluoxetine is an effective and well-tolerated form of treatment for Raynaud's phenomenon.

The absence of a placebo group is a significant weakness of this study, as substantial placebo effects have been observed previously in trials of treatments for Raynaud's phenomenon. However, the magnitude of the clinical effect in certain subgroups (e.g. a thermographic improvement of 54 and 76% in fluoxetine-treated females and primary Raynaud's patients respectively) suggests that this is more than a placebo response, because the placebo effect has been observed in other Raynaud's trials to be not more than 20%. Another potential limitation of this study is the relatively short duration of the washout period between treatment arms. It is possible that this was too short for fluoxetine owing to its long half-life, but a longer washout period would have introduced additional problems when comparing the two treatment periods.

Another limitation of the study is that it was open. This introduced potential biases and confounders but was necessary for essentially practical reasons. Objective thermographic and serological assessments were selected as robust end-points to supplement more subjective, though clinically relevant, self-reported symptom diaries, because of the open-label nature of the study.

Although patients were not formally assessed for any underlying depression, the alleviation of which might have accounted for at least part of fluoxetine's clinical effect as assessed by the subjective symptom diary records, we feel that it is unlikely that this was a major factor, as objective evidence of response was obtained from analysis of the thermographic data: significant improvement occurred in the same subgroups (female patients and patients with primary Raynaud's phenomenon) as those showing symptomatic benefit. This remains an important consideration because an improved mental attitude resulting from successfully treated depression might well influence responses in self reported diaries. Formal psychometric testing would be a valuable addition to any future study protocol.

This trial was conducted over one winter and, although there was a difference in ambient temperature between the beginning and the end of the study period, this potential bias was cancelled by the randomized cross-over design of the trial, which ensured that equal numbers of patients were assigned to fluoxetine and nifedipine at any particular period of the trial.

The calcium channel antagonist nifedipine was chosen in the cross-over arm of this trial because of its well established role in the treatment of Raynaud's phenomenon, as shown by several studies. .It was therefore surprising that in this trial there was no significant response, either symptomatic or thermographic, to nifedipine. This might have been partly due to the lower doses used (40 mg daily), as doses of 60 mg have been described in treating refractory Raynaud's phenomenon.

The relatively small number of patients evaluated in this pilot study means that subgroup analysis must be interpreted cautiously. However, it appears that patients with primary Raynaud's phenomenon responded better to fluoxetine, both symptomatically and thermographically, than the group of patients with an underlying connective tissue disorder. This might have resulted from the more advanced vasculopathy, with an element of irreversible structural damage, in patients with secondary Raynaud's phenomenon making them less amenable to pharmacological therapy.

One of the mechanisms by which fluoxetine may provide relief in Raynaud's phenomenon is by reducing the circulating level of serotonin, which is known to be a selective vasoconstrictor. Although platelets are a rich source of serotonin, they cannot synthesize it [21] but accumulate it throughout their physiological life. Normal plasma serotonin levels are very low [22] but rise when platelets aggregate [23]. Fluoxetine, which is an SSRI, blocks the uptake of serotonin into platelets [24] and will thus decrease the amount of serotonin that is released during platelet activation/aggregation. Fluoxetine is known to deplete platelet serotonin by 95% [25].

A difficulty encountered in recruiting for this trial-one that might pose a problem in clinical practice-was reluctance on the part of the patients to take an antiRaynaud's drug that is widely used as an antidepressant. Despite this, fluoxetine may occupy a useful niche in the treatment of this vasospastic condition because, apart from expanding the choice of drugs available, it has a low incidence of hemodynamic side-effects, which are often associated with the use of other vasodilators, such as the calcium channel blockers.

In conclusion, this pilot study has shown that the SSRI fluoxetine is generally well tolerated and an effective agent in reducing the severity and frequency of attacks of Raynaud's phenomenon. The response to treatment was variable and the greatest benefit was seen in female patients and patients with primary Raynaud's phenomenon. Some of the variability in the response to treatment may also have been due to genetic differences in metabolic or signalling pathways related to serotonin, and this possibility may be addressed in future studies. Larger and placebo-controlled trials are now warranted to assess fluoxetine further for its clinical efficacy and tolerability; if the results were favourable an important agent would be added to the therapeutic armamentarium in the often difficult management of Raynaud's phenomenon.

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