PAPERS AND ORIGINALS

Menopausal Flushing: Double-blind Trial of a Non-hormonal Medication

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Summary

A multicentre, placebo-controlled, double-blind, cross-over study conducted in general practice on 100 patients has shown clonidine to have a statistically highly significant effect in controlling the number and the severity and duration of menopausal flushes. The relatively mild side effects and the absence of potentially harmful oestrogenic effects suggest that clonidine in the dose range 25 to 75 μg twice daily is a useful addition or alternative to the existing therapy for this common symptom of the menopause.

Introduction

The hot flushes of the menopause can be difficult to treat. Non-oestrogenic compounds are often ineffective while oestrogens carry the small but real risk of potentially dangerous side effects. Though its underlying physiology remains obscure the condition is characterized by a peripheral vasomotor instability mainly affecting the "blush" areas with changes which are qualitatively similar, though in reverse order, to the vascular changes seen during an attack of migraine. The long-term administration of clonidine (2- (2, 6-dichlorophenylamino)-2-imidazoline hydrochloride; Dixarit) diminishes vascular reactivity (Zaimis and Hanington, 1969); consequently it is effective in the prophylaxis of migraine (Wilkinson, 1969; Shafer *et al.*, 1972). When used in considerably higher doses, as Catapres, however, it is a potent antihypertensive agent (MacDougall *et al.*, 1970), but with the small doses used in migraine prophylaxis no appreciable problems due to blood pressure reduction have been reported.

These facts led to a preliminary trial of clonidine in eleven unselected cases of menopausal flushing (Clayden, 1972). The results were very encouraging in all but two patients. They were confirmed in a separate open study by Williams (1973), who found that nine out of 13 patients benefited. During the discussion of results reported by Clayden 1973 it became evident that a carefully controlled further evaluation was needed. This paper presents the results of a placebo-controlled, double-blind, crossover, multicentre trial in general practice.

Patients and Methods

Patients were selected who suffered from menopausal flushing of sufficient severity to warrant treatment. Only those without other complicating illness and who could reasonably be expected to complete the trial were admitted. All previous medication for flushing, such as oestrogens, was stopped for at least two weeks before entry to the trial. Each patient participated for nine weeks. This period was divided into one week without treatment to obtain baseline values and to familiarize the patient with the procedure and two courses of treatment of four weeks each in which patients were randomly given the active drug or placebo as their first treatment. Neither patient nor doctor knew the order of medication.

Each attack of flushing was recorded by the patient on a diary card which was exchanged weekly. Patients were seen at nine predetermined times throughout the trial. At each visit, besides recording the number of flushes, questions were asked about the frequency, severity, and duration of attacks since the previous visit. The answers were recorded on a five-point scale from "much more" to "much less." Side effects were elicited by a simple question—for example, "Any problems with the tablets?" No direct questioning was used unless the patient was the first to mention side effects. Blood pressures and pulse rates were recorded at each visit.

Coded sets of record cards, diary cards, and tablets were supplied for each patient. White compressed tablets containing 25 μg clonidine or matching placebo tablets identical in appearance and taste were used. Treatment began with one tablet twice daily and increased to a maximum of three tablets twice

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daily depending on the effect or the presence of side effects. The patients were asked to return all unused tablets at each visit. These were counted and correlated with the number prescribed.

Out of 100 patients from 18 different practices 14 were excluded for various reasons (table I). The remaining 86 patients had a mean age of 50·4 years (range 41 to 62 years), a mean weight of 142 lb (range 98 to 190 lb) (64·6 kg; range 44·4 to 86·9 kg), and a median duration of flushing episodes before the trial of two years (range two weeks to 23 years). Forty-two patients received clonidine first. Of the 86 patients 10 did not take the prescribed number of tablets for part of the trial owing to external causes or because they misunderstood the instructions. In one of the 10 patients treatment was affected for two weeks but in the other 9 only one week was affected. The missed weeks were not included in the analysis.

TABLE I—*Reasons for Exclusion from Analysis of 14 Patients*

	No. of Patients	Treatment Discontinued	
		Clonidine	Placebo
Major discrepancy in tablet taking	4	—	—
Side effects	4	3*	1†
Spontaneous remission in first week	1	—	—
Other illness	2	2	—
Moved from area	1	—	1
Unwilling to continue due to lack of effect	1	—	1
Defaulted	1	—	1

*Leg pains and ankle swelling (see results).
†Collapsed unconscious.

Results

The number of flushes recorded by the patients showed an immediate placebo effect during the first treatment period. The mean number of flushes was therefore considered in two groups according to the first treatment received (table II). Also the change in the number of flushes between the initial treatment-free week and each subsequent week was calculated for each patient in both groups and the mean change for each week of active treatment and placebo (fig. 1) compared by two-way analysis of variance. For both groups of patients the reduction in the number of flushes throughout the period of clonidine treatment was significantly greater than the reduction during placebo treatment (clonidine before placebo P $\leq$0·05; clonidine after placebo P $\leq$0·001). The mean number of flushes for the combined clonidine treatments is compared with placebo in fig. 2.

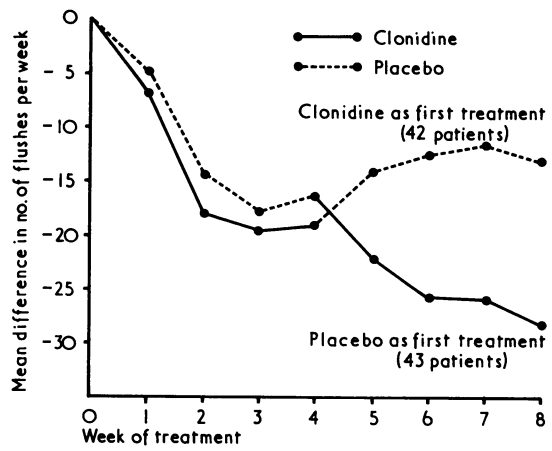

FIG. 1—Mean change in number of flushes from initial values.

The questions asked at each visit on the frequency, severity, and duration of flushes, though not so reliable as a count of the number of flushes, followed a similar pattern. If the patients had been asked the questions in relation to how they were at the beginning of the trial it would have been unlikely that by the end they could have recalled their initial condition reliably. The questions were therefore asked in relation to the previous visit and the score (on a five-point scale) was a guide to whether the patient believed she was improving. For each patient the response throughout the trial was determined by cumulating the positive or negative changes in condition (difference from the "no change" score of 3) at the end of weeks 1, 2, and 4 for the first treatment and weeks 5, 6, and 8 for the second treatment. The difference for week 1 was then compared with week 5 for each patient to see which treatment gave the better result. Similarly for weeks 2 and 6, 4 and 8 (table III). The sign test was used to determine statistical significance (Segal, 1956).

During the first treatment period more patients improved in all three parameters on clonidine compared with placebo. When patients received placebo as first treatment, however, clonidine still accounted for more improvements, but this did not achieve statistical significance owing partly to the placebo response and partly to some scores reaching maximum on placebo and re-

TABLE II—*Mean Number of Flushes in 42 Patients who received Clonidine First and in 43* Patients who received Placebo First*

	Clonidine as First Treatment									Placebo as First Treatment								
	Initial	Clonidine				Placebo				Initial	Placebo				Clonidine			
Week:		1	2	3	4	5	6	7	8		1	2	3	4	5	6	7	8
Mean	44·1	36·6	25·9	24·6	25·0	30·0	31·7	32·5	31·0	50·2	45·1	36·7	32·1	33·5	28·1	24·7	24·6	22·1
Mean change from initial Value		−7·5	−18·2	−19·5	−19·2	−14·2	−12·5	−11·7	−13·1		−5·1	−14·6	−18·1	−16·7	−22·1	−25·5	−25·7	−28·1
S.D.		14·9	23·9	23·1	25·0	19·5	19·8	21·0	23·3		20·3	31·3	32·3	34·5	35·8	34·7	35·9	36·7

*One patient was excluded from this analysis because diary cards for two weeks were incomplete.

TABLE III—*Comparison of Cumulative Changes in Score for Subjective Questioning of 41* Patients who received Clonidine First and 44 Patients who received Placebo First*

	Clonidine as First Treatment									Placebo as First Treatment								
	Frequency			Severity			Duration			Frequency			Severity			Duration		
Week:	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4	1	2	4
Clonidine score better	19	24	23	18	22	25	15	22	25	13	20	21	16	19	18	16	20	19
Scores the same	17	10	6	13	12	6	17	11	6	19	11	7	17	13	13	22	12	12
Placebo score better	5	7	11	10	7	9	9	7	7	12	13	16	11	12	13	6	12	13
P	0·01	0·01	0·1	N.S.	0·01	0·05	N.S.	0·01	0·01	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	0·1	N.S.	N.S.

*Results from o ne patient were incomplete.

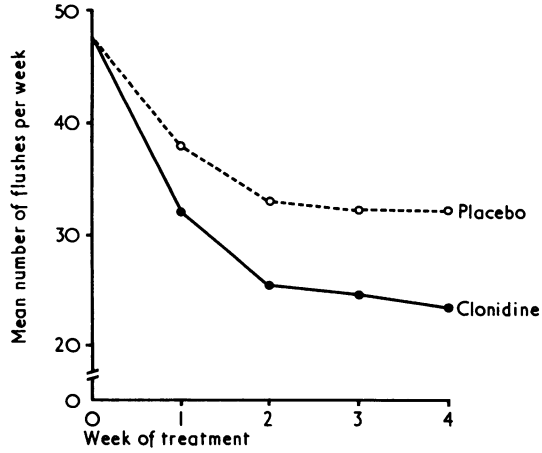

FIG. 2—Mean number of flushes per week.

maining at maximum throughout clonidine treatment so that the difference between treatments was not so distinct.

Duration of Menopause.—The duration of flushing before the trial ranged from two weeks to 23 years, which prompted a subdivision of patients into those who had had flushing for less and those who had had flushing for more than one year. Interestingly, those who had had flushing for more than one year had a far greater placebo response than those who had had flushing for less than one year. This emphasizes the psychological influences in a patient complaining of hot flushes over several years.

Blood Pressure.—There were no significant changes in the mean pulse rates and blood pressure values for either treatment (table IV). One patient who was hypertensive at the start of the trial completed both treatment periods before beginning specific antihypertensive treatment.

TABLE IV—*Mean Blood Pressure and Pulse Rate*

	Before Treatment	After One Week	Clonidine Week 1	Clonidine Week 2	Clonidine Week 4	Placebo Week 1	Placebo Week 2	Placebo Week 4
Systolic B.P. (mm Hg)	134	131	126	125	126	129	127	126
Diastolic B.P. (mm Hg)	83	82	78	77	78	80	80	79
Pulse (beats/min)	80	80	79	78	78	81	80	81

Dose.—As flushes ceased in only a few patients we should have expected the dose to reach three tablets twice daily in most patients, particularly those on placebo. Though this was the overall tendency more than expected did not receive the maximum dose. Fifteen patients on clonidine and 14 on placebo reached a dose of one tablet twice daily, 22 on clonidine and 21 on placebo reached a dose of two tablets twice daily, and 48 on clonidine and 50 on placebo reached a dose of three tablets twice daily. The pattern of response in each treatment group was similar for each dose but the patients who remained in the lower dose groups had proportionately fewer attacks and a milder condition at the start of the trial, which, together with the multitude of reported side effects, must have influenced the prescribing pattern.

Side Effects.—A variety of side effects were reported, which was expected considering the large functional element believed to play a part in this condition. Of 100 patients 56 reported side effects and of these 34 reported them on clonidine and 36 on placebo. The side effects were, however, mostly nonspecific and, with the possible exception of dry mouth, well distributed between the placebo and active treatment periods (table V).

TABLE V—*Side Effects reported by 56 Patients*

	Clonidine	Placebo
Central nervous system:		
Insomnia, drowsiness, depression, anxiety, disorientation, visual disturbances, headache, vertigo, hysteria	22	22
Dry mouth	11	5
Other gastrointestinal:		
Indigestion, nausea, abdominal pain, constipation, bloated sensation	12	9
Skeletal:		
Cramp, leg pains, backache	5	5
Cardiovascular:		
Palpitation, tachycardia, hot/cold sensations, flushes caused by tablets	4	7
Skin:		
Itching, rash, sweating, hair loss	7	4
Genitourinary:		
Vaginal discharge, pain on micturition	1	1
Collapsed unconscious		1

Of the four patients excluded because of side effects (table I) the symptoms of leg pains and ankle swelling in three were difficult to explain. The patients were all from the same practice but it was thought improbable that they had conferred. No cause could be found and, in particular, no evidence of deep vein thrombosis. Though all three were taking clonidine when withdrawn symptoms developed in one while on placebo. A relation to clonidine was uncertain, and similar side effects have not been reported elsewhere.

Discussion

In most cases hot flushes are the most important and disturbing symptom of the menopause. Their management, however, is fraught with difficulties. Often strong psychological and emotional influences accompany the physiological changes. Jeffcoate (1969) stated that of the 25% of women who seek medical advice 5-10% need only reassurance. Hazan and Conneely (1964) also comment that simple reassurance alone may alleviate vasomotor symptoms and that management should aim to remove emotional stress as well as treat vasomotor instability. In this situation, therefore, irrational responses can easily create problems in the evaluation of a new drug.

During this study a pronounced placebo response was seen. This was predictable considering the condition and the type of patients. When placebo replaced active treatment the baseline number of flushes was not regained, which, besides placebo response, must reflect both a continuous improvement in condition with time and probably the benefit of the increase in attention received during the trial. This contrasts with another recent investigation of a new treatment (Utian, 1973) in which no placebo response was found. There was a difference, however, in that the flushes in the patients investigated were associated with hysterectomy and bilateral oophorectomy rather than the natural menopause, which may partly accord with our finding of a lower placebo response in women who had begun flushing less than one year before the start of the trial.

Clonidine in higher doses is used for the treatment of hypertension, but despite the more labile vasculature of our patients no problems were caused by changes in blood pressure and pulse rate. All other medication, so far as possible, was stopped before admission to the trial, though in Clayden's (1972) original trial four patients were receiving hormone therapy when clonidine was begun and no unwanted effects were reported from the combination. Clonidine, however, will only modify the vascular response and will not correct other changes due to hormonal deficiencies.

We have confirmed the finding of Zaimis and Hanington (1969) that clonidine reduces the response of small blood vessels to various stimuli. The use of a double-blind crossover technique has more readily demonstrated the action of clonidine in this situation compared with the trials in migraine, probably because of the much greater frequency of flushing attacks. The fact that the drug has no overt effects on hormonal balance may help us

to understand the true aetiology of menopausal flushes. It has been realized for some time that there is no clear connexion between the hormone levels in blood and urine and severity of flushes. The events at vascular level have never been fully investigated—in fact, the recent bibliography on the menopause is remarkably short. We hope that the present report will stimulate further investigation of menopausal vasomotor symptoms and of factors that precipitate them, so that they may be related more closely to other vasomotor disorders.

We may state in conclusion that clonidine, in doses similar to those used for migraine prophylaxis, seems a useful and safe alternative or even addition to other treatments for hot flushes and that it has no important side effects.

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Specific Laboratory Test for Diagnosis of Multiple Sclerosis

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Summary

Lymphocytes from patients with multiple sclerosis are much more susceptible to the inhibitory activity of linoleic acid (0·08 mg/ml) when tested for sensitization to thyroid by the macrophage electrophoretic mobility test (91% inhibition) than are those from normal subjects (57% inhibition). Cells from patients with a variety of other neurological diseases give 47% inhibition with linoleic acid. These differences are specific for multiple sclerosis and can be used as an in-vitro diagnostic test for the disease. Nearly 43% of clinically normal near relatives of patients with multiple sclerosis show an "anomalous" figure of about 77%; in the remainder the figure is the same as in the general population (57%). An anomalous result is compatible with lifelong freedom from M.S. Possibly a congenital anomalous handling of unsaturated fatty acids is a constant feature of the disease.

Introduction

While most cases of multiple sclerosis (M.S.) present little difficulty in diagnosis there are instances in which it must be left tentative, and the lack of some specific diagnostic in-vitro test is acutely felt. Lymphocytes from patients with M.S. are much more severely depressed by linoleic acid in their recognition of antigen than are those from patients with other neurological diseases or from normal subjects (Mertin *et al.*, 1973). This difference is sufficiently consistent to constitute a specific diagnostic test for M.S.

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Subjects and Methods

Four groups of subjects were studied—(1) 33 patients with M.S., of whom all except one were in a quiescent phase of the disease; (2) 27 patients with other neurological diseases; (3) 46 normal subjects aged 22 to 59 years drawn from the general population (not matched for age and sex); and (4) 96 relatives of M.S. patients, all of whom were clinically without neurological disease. This group comprised fathers, mothers, sons, daughters, brothers, sisters, nephews, and nieces of patients. In addition a few grandparents and grandchildren were studied.

Lymphocytes were prepared from 10-15 ml venous blood by the methylcellulose and carbonyl iron method of Coulson and Chalmers (1967) as modified by Hughes and Caspary (1970). Lymphocytes from normal subjects (Field *et al.*, 1970) as well as from those with a variety of diseases—for example, cancer, sarcoidosis, M.S., and other neurological diseases—interact with thyroglobulin (F1 fraction of thyroid). Indeed no subject has been seen (save with early measles infection) who did not respond fully to thryoglobulin, so that this may be used as a universal test antigen for measuring lymphocyte-antigen interaction. (Cells from chimpanzees, rhesus monkeys, sheep, and guinea-pigs also react with human thyroglobulin.) There is also almost universal sensitization of human lymphocytes (in Britain) to P.P.D. (purified protein derivative of tuberculin)—again with the exception of measles—only three out of several hundred tests giving negative results. Lymphocytes with M.S. or other neurological diseases react with encephalitogenic factor (Caspary and Field, 1970). In all these studies the method used was the macrophage electrophoretic mobility test (Field and Caspary, 1970), a detailed account of which, together with a protocol in extenso, has been published (Caspary and Field, 1971).