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(*Accepted 11 June 1985*)

Efficacy of feverfew as prophylactic treatment of migraine

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Abstract

Seventeen patients who ate fresh leaves of feverfew daily as prophylaxis against migraine participated in a double blind placebo controlled trial of the herb: eight patients received capsules containing freeze dried feverfew powder and nine placebo. Those who received placebo had a significant increase in the frequency and severity of headache, nausea, and vomiting with the emergence of untoward effects during the early months of treatment. The group given capsules of feverfew showed no change in the frequency or severity of symptoms of migraine. This provides evidence that feverfew taken prophylactically prevents attacks of migraine, and confirmatory studies are now indicated, preferably with a formulation controlled for sesquiterpene lactone content, in migraine sufferers who have never treated themselves with this herb.

Introduction

Feverfew (*Tanacetum parthenium*) is a medicinal herb commonly used in self treatment for conditions such as migraine and arthritis. In one survey more than 70% of 270 migraine sufferers who had eaten feverfew leaves every day for prolonged periods claimed that the herb decreased the frequency of the attacks or caused them to be less painful, or both.[1] Many of these people had failed to respond to orthodox medicines. Although possible mechanisms of action have been proposed for the beneficial effects of feverfew,[2-4] no one appears to have questioned whether it is in fact clinically effective in any condition.

From a large number of migraine sufferers known to the City of London Migraine Clinic to be treating themselves with feverfew 20 were invited to enter a double blind study, aware only that they might be treated with either active dried feverfew or placebo.

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Patients and methods

We aimed to recruit 20 patients who had been treating themselves with raw feverfew leaves every day for at least three months. Ten patients were to receive active treatment consisting of freeze dried, powdered feverfew leaves in capsule form and 10 placebo. The patients had to have a history of common or classical migraine of at least two years' duration with no more than eight attacks a month at the time of admission.

We had intended to exclude patients who had taken the following drugs within one month of the study: tranquillisers, α blockers, β blockers, antidepressants, non-steroidal anti-inflammatory agents, or clonidine and pitzotifen used prophylactically. In the event we decided that this criterion could be waived if patients had begun prophylactic treatment with one of these drugs before starting to use feverfew daily, and provided that those taking antidepressants or tranquillisers showed no signs of current mental illness.

Before admission the nature and purpose of the study, including possible benefits and problems, were explained to each patient by one of us (ESJ), and the patient's informed consent to participate was obtained. Three patients refused to participate because they feared the possible consequences of being assigned to the group receiving placebo. The study was approved by the ethical committee of the City and Hackney District Health Authority.

Trial design—The trial was a double blind, placebo controlled comparison between two groups. Successive patients who had suffered from classical or common migraine for at least two years were allocated randomly to receive either feverfew or identical placebo capsules in numbered packs. Patients were instructed to take two capsules every morning with food for six periods of four weeks. They were instructed to treat acute attacks of migraine with soluble aspirin or their usual drug.

Diary cards—Patients were instructed how to record the various visual symptoms, nausea, vomiting, and headache (including times of onset and relief and any additional treatment) and to grade them according to severity on diary cards provided for each period. The severity of nausea or vomiting was recorded as: 0 = neither nausea nor vomiting; 1 = nausea only; 2 = vomiting, single episode; 3 = vomiting, repeated episodes. Headache was scored: 0 = no pain; 1 = mild, unpleasant but not affecting work or recreational activities; 2 = severe, reducing ability to work or carry out recreational activities; 3 = incapacitating, unable to work or carry out recreational activities; 1 = duration up to six hours; 2 = duration between six and 24 hours; 3 = duration greater than 24 hours. Presence of usual visual disturbance scored 1. Use of drugs was scored: 1 = use of repeated doses of minor analgesics; 1 = use of single dose of ergotamine; 2 = use of repeated doses of ergotamine. The cards were reviewed at intervals of one to two months throughout the study.

Preparation of feverfew capsules and dosage—Each freeze dried leaf containing five leaflets weighed a mean (SEM) of 25·7 (0·7) mg (n = 52). The mean daily dose of feverfew used by patients before entry to the study was 2·44 leaves (roughly 60 mg). We therefore decided that the dose of each capsule should be fixed at 25 mg and that each patient should receive two capsules daily. Preparation of the opaque capsules of hard gelatin (Eli Lilly, size 2) was supervised by DMH and PJH,

and production of the capsules at Chelsea College was approved by the Department of Health and Social Security. The contents of the placebo capsules were matched for colour with the active capsules with chlorophyll. The feverfew used was grown in the Chelsea Physic Garden and harvested in a single batch in September. The contents of the bottles were sprinkled with a small amount (1-2 mg) of feverfew powder so that on opening both active and placebo capsules gave identical smells.

Safety tests—Patients were asked to donate sufficient venous blood for routine analysis of its cellular and chemical elements and to provide a sample of urine for routine analysis (pH; excretion of bilirubin, blood, and glucose; and sediment).

Statistical analysis—Non-parametric statistical methods such as the Wilcoxon rank sum test were used for comparisons between the treatments and the Wilcoxon matched pairs signed ranks test for comparisons within the groups of frequencies of headache, nausea, vomiting, global assessment of efficacy, and correct detection by patients of the treatment that they were receiving. Parametric *t* tests were used as appropriate for quantitative measurements such as blood pressure, heart rate, and weight.

Results

Characteristics of patients on admission—Eight patients (mean age 44·9 (SEM 4·2) years) received feverfew and nine (mean age 51·2 (2·3) years) received placebo capsules. The patients in the active group had taken 2·44 (0·2) small leaves of feverfew daily for 3·38 (0·58) years before entry to the study, and those in the placebo group had taken 2·33 (0·48) small leaves daily for 4·18 (0·67) years. Thus the two groups did not differ in the amount of feverfew consumed daily or the duration of consumption. The two groups also did not differ significantly in their recollection of the frequency of migraine before self treatment with feverfew (*t* test or Wilcoxon's rank sum test, $0{\cdot}1 > p > 0{\cdot}05$). Patients in the active group claimed that they had suffered 7·44 (1·33) attacks each month before self treatment with feverfew and that during self treatment the monthly rate had fallen to 1·63 (0·73) attacks (table I), whereas those in the placebo group had suffered only 3·94 (1·08) attacks each month before self treatment with feverfew and 1·22 (0·54) during self treatment. The reduction in the frequency of migraine during self treatment was significant for both groups (Wilcoxon's matched pairs signed rank test: feverfew group $p < 0{\cdot}05$, placebo group $p < 0{\cdot}01$). Thus when the two groups were recruited to the study their mean numbers of attacks each month were similar.

Concomitant drugs taken throughout the study—One patient in each group was taking conjugated equine oestrogens (Premarin); the patient in the placebo group was also taking pizotifen. One patient given feverfew was taking the combined oral contraceptive Orlest 21. One patient in each group was taking a diuretic: the patient given feverfew was also taking clorazepate and the patient given placebo was also taking a product containing tranylcypromine and trifluoperazine. In addition, two people in the placebo group were taking vitamin preparations and one prochlorperazine.

TABLE I—*Monthly frequencies of headaches suffered by patients before and during study*

Case No	Before taking feverfew leaves	While taking feverfew leaves	During study: Mean of 6 months	During study: Mean of 4th-6th months
		Patients given feverfew		
1	12	0	0	0
2	8	1	1	2
3	1-2	2	0·83	0
4	6	6	5·33	5·33
5	12	1	2	2
6	8-12	0	2	1·67
7	6	0	2	1·67
8	4	3	1·33	0·33
Mean (SEM)	7·44 (1·33)	1·63 (0·73)	1·69 (0·57)	1·50 (0·62)
		Patients given placebo		
9	2	0-1 (occasional)	1·67	2
10	1	0-1	1·17*	2·33*
11	8-12	3	7·5	9
12	4	3	5·67	4·33
13	1-2	0	1·33	2·67
14	4	0	4†	Withdrawn
15	4-12	4	3·33*	3‡
16	1-8	0	3†	Withdrawn
17	0·5	0	0·5*	0·67‡
Mean (SEM)	3·94 (1·08)	1·22 (0·54)	3·13 (0·77)	3·43 (1·02)

*Additional headaches reported by patient but not detailed on diary card.
†Three months only.
‡Headaches too numerous to be recorded separately.

TABLE II—*Distribution of patients according to total number of months during which they considered themselves to be taking active medication*

Treatment	Total No of months: 0	1	2	3	4	5	6
Active (n = 8)			1		1	1	5
Placebo (n = 9)	5	2	1	1			

$p < 0{\cdot}001$ (Wilcoxon's rank sum test).

TABLE III—*Distribution of nausea and vomiting according to incidence and severity during treatment with feverfew and placebo. (Figures are numbers (%) of attacks of migraine in which nausea and vomiting occurred)*

	Treatment with feverfew (n = 93)	Treatment with placebo (n = 147)
Nausea	34 (37)	95 (65)
Vomiting, single episode	2 (2)	13 (9)
Repeated vomiting	3 (3)	8 (5)
Total	39 (42)	116 (79)

Frequency of migraine—Fewer headaches were reported in each month by patients taking feverfew capsules than by those taking placebo (table I). In fact, there was considerable underrecording by three patients taking placebo (cases 10, 15, and 17), who reported frequent headaches at the monthly or bimonthly interviews but did not record them on the diary cards, which therefore rendered statistical analysis difficult. In cases 15 and 17 the patients did not record mild or severe headaches unless they identified them, in conjunction with other symptoms, as true migraine. The patient in case 10 suffered on average three mild headaches a week until month 5; these were particularly noticeable during months 3 and 4. Two patients withdrew themselves from the study (cases 14 and 16) because of recurrent severe migraine and, in case 14, other symptoms which the patient was not prepared to tolerate, including disturbed sleep and stiffness in the joints of the fingers, shoulders, and knees in the morning. Both of these patients were subsequently found to be receiving treatment with placebo and resumed treatment with feverfew leaves with subsequent alleviation of symptoms. Table I gives the mean monthly frequencies of headaches, regardless of severity, during the trial in both groups. Comparative data are given for the whole six months and also for the final three months to exclude any carryover effects in the placebo group during the initial months of the study. The patients taking feverfew experienced 1·5 (0·62) attacks a month during the final three months (1·69 (0·57) over the six months), which was identical with the frequency of attacks when they were taking raw leaves. On the other hand, the frequency in patients taking placebo increased to 3·43 (1·02) attacks a month in the final three months (3·13 (0·77) over the six months), which was significantly higher than the frequency when these patients were taking raw feverfew leaves ($p < 0{\cdot}02$). In fact, the frequency of headaches in the patients taking placebo was almost identical with that reported by these patients before they began self treatment with feverfew leaves.

Guessing of treatment received—Patients were asked to guess each month which of the two treatments they were receiving. Table II shows that most patients consistently guessed correctly.

Incidence and severity of nausea and vomiting—Table III gives the total number of bouts of nausea and vomiting for both groups. Nausea or vomiting, or both, occurred on only 39 occasions in the group given feverfew compared with 116 in the placebo group. This difference was significant ($p < 0{\cdot}05$). Furthermore, only 42% of the attacks of migraine recorded by patients taking feverfew were associated with nausea and vomiting, compared with 79% of those recorded by patients taking placebo. This difference was also significant (Wilcoxon's rank sum test, $p < 0{\cdot}05$).

Consumption of minor analgesics and ergotamine—The amount of analgesics consumed is sometimes used to indicate the severity of migraine. As the patients taking placebo suffered more attacks their consumption of analgesics was expected to be greater. Only paracetamol, however, was found to be used more by patients in the placebo group (table IV). When the amounts used for each attack were

TABLE IV—*Analgesics and ergotamine tartrate taken for migraine by patients taking feverfew or placebo*

Patient group*	Drug	No of tablets consumed	Total weight consumed (g)	No (%) of attacks in which drug was used	mg Taken during each attack treated with analgesics
Feverfew (93 attacks†)	Paracetamol	10	5	6 (7)	833
	Aspirin	113	33·9	32 (35)	1130
	Ergotamine (Migril)	46	0·092	52 (56)	1·88
Placebo (147 attacks)	Paracetamol	186	93·0	78 (53)	1274
	Aspirin	104	31·2	29 (20)	1156
	Ergotamine‡	64	0·128	80 (54)	1·71

*Each group comprised 48 patient months.
†81 associated with headaches.
‡Migril tablets (102 mg) and Cafergot suppositories (26 mg).

calculated it was found that the same doses of aspirin and ergotamine were used by both groups but that the amount of paracetamol used by patients taking placebo was substantially greater. This finding is consistent with the disproportionately greater number of severe and incapacitating attacks in this group, but the possibility that it may also reflect the patients' preference before they entered the study cannot be excluded.

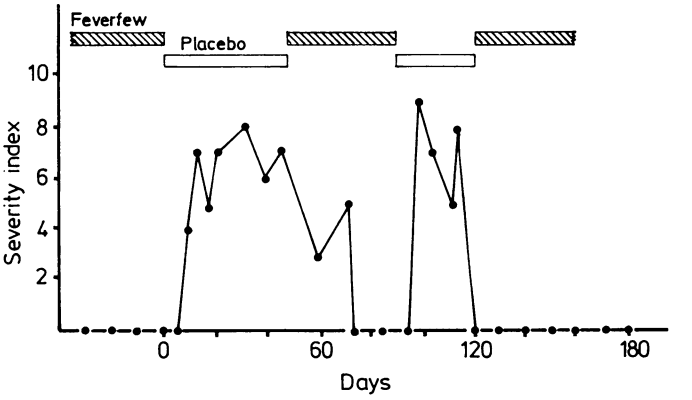
Global assessment of efficacy—At the end of the trial patients were asked for their comments on the treatment they had received. More people in the active group preferred their capsules, although there was some overlap. One patient with classical migraine who was taking feverfew noticed that, although his headaches and vomiting were completely abolished, his visual symptoms continued to trouble him. This has been reported by several users[5]; these refractory auras usually respond to a modest increase in the dose of feverfew. Patients were invited to assess the overall effect of their treatment on a six point scale; table V shows their responses. Six patients in the active group claimed that the capsules had an effect varying from moderately good to excellent, whereas only three did so in the placebo group. The distribution of these responses was significantly different (Wilcoxon's rank sum test, $p < 0.01$).

TABLE V—*Overall clinical efficacy of treatment as judged by patients*

Effect of treatment	Feverfew	Placebo
None		4
Poor		2
Fair	2	
Moderately good	1	2
Good	2	1
Excellent	3	

$p < 0.01$ (Wilcoxon's rank sum test).

Discontinuation of feverfew—The abrupt discontinuation of consumption of feverfew after several years' use led to the recurrence of incapacitating migraine in some patients. Two women (cases 14 and 16), whose migraine was in complete remission during self treatment with feverfew leaves, could not bear to complete the study and withdrew from it to resume consumption of raw feverfew. The patient in case 14 (figure) had had no attacks while taking two or three small leaves of feverfew (roughly 75 mg dried powder) daily for four and a half years. When the feverfew was replaced by placebo for six weeks she suffered severe migraine, which stopped only when she withdrew from the trial and resumed self treatment. Six weeks later she again agreed to take the capsules, whose contents remained unknown to her. The recurrence of extremely severe migraine caused her to withdraw from the study again and revert to her daily regimen. She had no attacks of migraine in the subsequent six months. The patient in case 16 had had no attacks during the six months before entering the study. She had had an average of two or three attacks a year during the four years in which she consumed one small leaf (roughly 25 mg dried powder) daily. While taking placebo she had her first attack after 13 days, but when she resumed self treatment with the leaves attacks gradually decreased in severity before disappearing completely. The slower rate of decrease in severity experienced by this patient when she resumed treatment with feverfew compared with that in case 14 probably reflects the fact that the patient in case 14 was taking three times the "dose" of this patient. Eight months after the study she was still free of migraine while consuming feverfew equivalent to only 5 mg dried powder daily.



Reversal by placebo of suppression of migraine attacks induced by feverfew in a woman aged 62 suffering from classical migraine. Severity index was scored from entries on patient's diary card.

Effects of feverfew on the cardiovascular system—Before treatment the mean blood pressure (sitting) in the patients in the feverfew group was 134/86 mm Hg; after six months of treatment it was 125/82 mm Hg. The corresponding values in those in the placebo group were 122/80 mm Hg and 120/82 mm Hg. Although the two groups differed significantly in their systolic blood pressures before treatment, there were no significant differences between them after six months of treatment. This is particularly important in the group taking placebo, in which both systolic and diastolic blood pressures were almost identical before and at the end of treatment. There were no significant changes within the groups (paired t test). Although heart rates before treatment were similar in the two groups, the heart rates in the group given feverfew were significantly higher ($p < 0.05$) at the end of treatment, a result accounted for by two patients (cases 4 and 5) whose heart rates were 26 and 20 beats higher at the end of treatment.

Effect of feverfew on body weight—Mean body weights did not change significantly throughout the six months of the study, with a mean decrease of 0·6 kg in the group given feverfew compared with an increase of 0·2 kg in the placebo group.

Adverse events—All patients taking placebo reported at least one event (table VI), whereas four patients taking feverfew reported none.

TABLE VI—*Adverse events*

Symptom	Patients given feverfew	Patients given placebo
None	4	
Nervousness, tension, less calm, jumpy		5
Tension or frequent non-migrainous headaches		3
Insomnia, disturbed sleep, nocturnal restlessness		2
Stiffness or pain in joints	2 (always had it)	3 (new occurrence)
Tiredness		2
Nausea		1
Lighter, irregular periods		1
Slightly heavier periods	1	1
Palpitations	1	
Colicky abdominal pain	1	
Urinary frequency		1

The events in the placebo group were related to the central nervous and musculoskeletal systems and included feelings of nervousness, tension, tension headaches, insomnia or disturbed sleep, and tiredness. Three of these patients also experienced pain or stiffness in the joints. These symptoms were particularly serious during the first two months of placebo treatment but lessened subsequently. None of these symptoms were experienced by patients taking feverfew. The two patients taking feverfew who complained of stiffness in the joints had suffered this throughout their self treatment with raw leaves.

Results of laboratory tests—Blood was taken for full haematological and biochemical analysis on enrolment and at the end of the trial. Complete data were obtained for eight patients in each group. No blood was taken from one patient (case 16) during treatment with placebo as she withdrew after the third month and was again taking feverfew by the time of her subsequent visit to the clinic. The blood obtained in case 14 was taken at the end of period 4, just before the patient withdrew from the study for the second time. There were no

differences within or between the groups in the incidence of abnormal laboratory findings or in changes of values from normal to abnormal and vice versa.

Discussion

In recent years, after newspaper reports of successful responses in sufferers resistant to conventional treatments, patients with migraine and arthritis have turned to the herb feverfew.[1 6] Although most users eat fresh leaves, the health food industry has responded rapidly to the demand for tablets and capsules containing dried feverfew. The development of most of the available tablets and capsules has not, however, been based on clinical observation or clinical trials, and several "high dose" products have been introduced, which contain up to four times the amount of feverfew that has been taken daily by most users.

Analysis of detailed questionnaires completed by some 300 users yielded considerable information about migraine sufferers who turn to feverfew.[1 5] Users ate one to four small fresh leaves every day, usually with food to mask the plant's bitter flavour. Five of every six users were women, and the information provided indicates that 88% suffered from true migraine. They resembled other patients with migraine in all respects except that their condition tended not to respond to conventional medicines.[5] Three quarters of all users questioned had never taken other herbal remedies and, of those who said they had, many had in fact taken vitamin preparations which could not be classed as herbal products. Nearly all patients had taken medicines prescribed by their doctors—for example, 75% had taken ergotamine at some time. Comparatively few of the people surveyed had found preventive medicines helpful and, even if they had, two thirds had no longer found them necessary once they started taking feverfew. When the responses of patients who were suffering only from migraine and not taking preventive drugs of any kind were analysed 72% claimed that their headaches were less frequent or painful, or both; 24% thought that they were unchanged; and 2% considered that they were made worse by taking feverfew.

The criticism that data obtained from the responses to questionnaires completed by a self selected population of users of feverfew may be unreliable and not represent a true picture of the efficacy of this plant is difficult to counter. Most people had learnt of feverfew from newspapers or from other users. They were therefore aware of the possible efficacy (but not, generally, the side effects) of the treatment and the delay in the onset of the beneficial response. Some of the answers to the checklist of symptoms in the questionnaire[5] were therefore possibly influenced by what the subjects knew of other users. The information gained, however, certainly indicated that further examination using a more sophisticated experimental approach was warranted: the patients might have discovered an effective herbal treatment. Thus the present pilot trial was designed to establish whether evidence of efficacy could be obtained by orthodox clinical evaluation and whether there were any demonstrable adverse effects on the cellular and chemical elements of blood. The possible ethical objection to giving patients treatment that had been incompletely tested was obviated by including only those already taking the leaves. In view of the self selected nature of the group under examination the results could never do more than suggest that other patients with migraine would or would not benefit from the treatment.

The mean frequency of attacks of migraine in those who were given placebo increased from the low level of 1·22 attacks each month during self treatment to three times this number, which was the number suffered before self treatment. Those who took capsules containing powdered feverfew showed no change in the frequency of their attacks. Two people taking placebo capsules withdrew from the study to resume use of raw feverfew leaves. The severe attacks of migraine that they suffered while taking the placebo were prevented when they resumed treatment with the leaves.

Far fewer severe and incapacitating headaches were recorded by the patients taking feverfew than by those taking placebo. The patients taking feverfew also suffered a far lower incidence of nausea and vomiting (39 reports compared with 116 in the placebo group). Furthermore, only 42% of attacks of migraine recorded by patients taking feverfew were associated with these symptoms compared with 79% of those experienced by patients taking placebo.

The global assessment made by patients at the end of the trial showed that significantly more patients given feverfew thought that they had benefited from treatment. Dried feverfew capsules did not appear to affect blood pressure, heart rate, body weight, or the results of haematological and biochemical tests, but there was one report each of transient palpitations, colicky abdominal pain, and heavier menstruation. Stiffness in the joints was reported by two patients taking feverfew but was not considered to be due to treatment as the patients had had the condition before starting self treatment.

The distribution of adverse events differed greatly between the two groups. All patients given placebo reported at least one event. There were five reports of increased nervousness, three of tension headaches, two of insomnia or disturbed sleep, and three of stiffness in the joints. We believe that these effects constitute a genuine "postfeverfew syndrome" as when 164 users who had stopped taking feverfew were asked to describe their symptoms about one tenth complained of moderate to severe aches, pains, and stiffness in joints and muscles together with central nervous system symptoms of anxiety and poor sleep.[5]

The users of feverfew who were admitted to this study had tolerated the daily intake of leaves well and complained only of the herb's disagreeable flavour. The absence of adverse events in such a self selected population is to be expected, but it does not reflect the true incidence of untoward effects, as when 300 users were questioned 18% reported adverse events, the most troublesome of which was ulceration of the mouth, experienced by some 11·3%. Feverfew also sometimes induces a more widespread inflammation of the oral mucosa and tongue, often with swelling of the lips and occasionally with loss of taste. The mouth ulcers may be a systemic effect of feverfew as, in a different study, ulceration in a patient taking feverfew tablets resolved when the drug was changed (unknown to the patient) to placebo but returned on rechallenge with the active tablets. The generalised soreness of the mouth may be caused by direct contact with the leaves during chewing and is possibly attributable to their sesquiterpene lactone content, as these compounds cause contact dermatitis.[7]

The mechanism of action of feverfew in migraine is not known. The plant is rich in sesquiterpene lactones,[8] the principal one being parthenolide, which was first isolated by Sorm and coworkers.[9] Several new biologically active members of this group have been isolated,[8 10] some of which are spasmolytic in that they render smooth muscle non-selectively less responsive to endogenous substances such as noradrenaline, acetylcholine, bradykinin, prostaglandins, histamine, and serotonin in a non-competitive manner (N Kumar, E S Johnson, unpublished findings). These antagonist properties are consistent with an antimigraine effect through inhibition of the influx of extracellular calcium into vascular smooth muscle cells. Another possible mechanism of action was suggested by Makheja and Bailey, who found evidence that aqueous extracts of the plant inhibited the activity of purified human platelet phospholipase A_2,[2 3] although the recent experiments of Heptinstall *et al* point to an effect of feverfew on activation of protein kinase C.[4]

The question of whether feverfew is safe for long term use remains. Certainly the laboratory findings in these 17 patients showed no important abnormalities before treatment with the capsules was begun and no differences between the two groups at the end of the six months of study. The fact remains, however, that no studies of chronic toxicity have yet been performed on the plant. Indeed, it could be argued that the usual toxicity tests in animals lasting six months are now superfluous because feverfew has been used by large numbers of people continuously for

many years (more than 10 years in some cases). Given the variation in sesquiterpene lactone content between varieties of feverfew and plants harvested in different seasons (P J Hylands, unpublished findings), it would seem desirable for commercial preparations of feverfew to be standardised chemically.

We thank the curator, Chelsea Physic Garden, for the feverfew; Sister Joan Vincent, of the City of London Migraine Clinic, for her help with the administration of this study; Miss Fiona Monaghan for her help with the preparation of this manuscript; and Dr K D MacRae, reader in medical statistics at the Charing Cross and Westminster Medical School, for statistical advice and for undertaking an independent evaluation of these results. A grant from the British Migraine Association to meet the travelling expenses of some patients is also gratefully acknowledged.

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(*Accepted 25 May 1985*)

SHORT REPORTS

Plasminogen activator inhibitor in the blood of patients with coronary artery disease

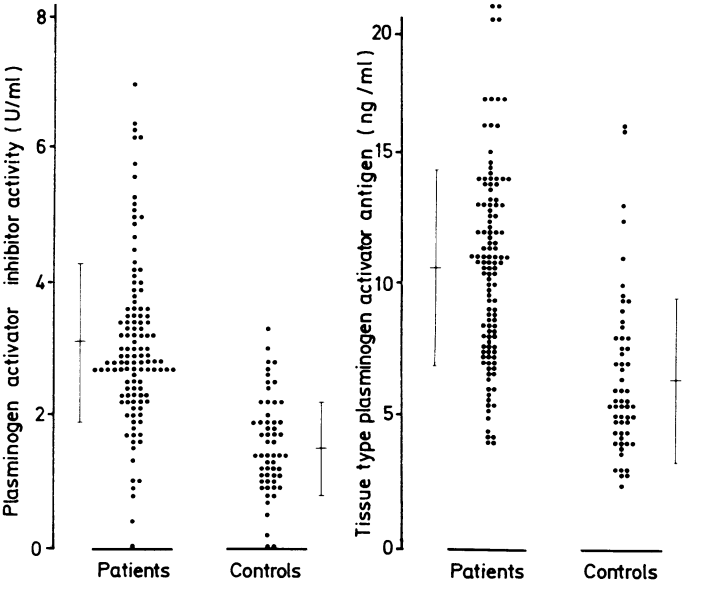
Impairment of fibrinolytic activity in blood has been claimed to contribute to the development of coronary artery disease and myocardial infarction.[1] Human plasma contains a fast acting inhibitor of tissue type plasminogen activator, which may have a primary role in the regulation of the fibrinolytic system.[2] Increased activity of this plasminogen activator inhibitor has been found in clinical and experimental conditions associated with reduced fibrinolytic activity and thrombotic phenomena.[3 4] We studied the activity of plasminogen activator inhibitor in the plasma of patients with angiographic evidence of coronary artery disease.

Patients, methods, and results

We studied 118 patients (92 men and 26 women, aged 35-70) with angina pectoris who were admitted for coronary angiography and in whom stenosis of the coronary artery was documented. Coronary angiograms were evaluated using a computer assisted reporting system.[5] An overall score of the severity of the coronary lesions was calculated, which took into account the graded narrowing, length, number, and site of the different stenoses. On the basis of this evaluation three patient groups were distinguished: patients with slight coronary lesions (coronary severity score <25; $n=45$); patients with moderate lesions (coronary severity score 26-50; $n=50$); and patients with severe lesions (coronary severity score >50; $n=23$). Twenty six patients were taking β adrenergic blockers at the time of angiographic evaluation. Blood samples were collected on trisodium citrate (0·011M final concentration) on arrival at the hospital. Plasma was immediately prepared by centrifugation (20 minutes at 1500 *g*) and stored at −70°C. A control group matched for age consisting of 57 apparently healthy subjects (31 men and 26 women, aged 40-64) was studied simultaneously. Plasma euglobulin fibrinolytic activity was measured with the fibrin plate method, tissue type plasminogen activator related antigen by a two site immunoradiometric assay, and activity of plasminogen activator inhibitor with an amidolytic assay.[4]

Significantly increased activity of plasminogen activator inhibitor (3·1 (SD 1·2) U/ml *v* 1·5 (0·7) U/ml, $p<0·001$) and concentrations of tissue type plasminogen activator antigen (10·6 (3·7) ng/ml *v* 6·4 (3·1) ng/ml, $p<0·001$) were found in the patients compared with the controls (figure); plasma euglobulin fibrinolytic activity was, however, not significantly different (0·8 (0·3) IU/ml *v* 0·9 (0·2) IU/ml). The activity of plasminogen activator inhibitor and concentration of tissue type plasminogen activator antigen were not significantly different in the three groups of patients with different degrees of coronary lesions.

No correlation was found between plasma activity of plasminogen activator inhibitor and either the concentration of tissue type plasminogen activator antigen or the euglobulin fibrinolytic activity. Plasminogen activator inhibitor activity did not correlate with cholesterol and high density lipoprotein cholesterol concentrations and was not different in patients taking β adrenergic blockers. Finally, there was no difference related to sex in the plasminogen activator inhibitor activity or the concentration of tissue type plasminogen activator antigen either in the patients (3·0 (1·3) U/ml in men *v* 3·3 (1·2) U/ml in women, and 10·7 (3·8) ng/ml *v* 9·8 (3·2) ng/ml) or in the controls (1·5 (0·7) U/ml *v* 1·5 (0·7) U/ml, and 7·0 (3·0) ng/ml *v* 6·0 (3·1) ng/ml).



Activity of plasminogen activator inhibitor (left) and concentration of tissue type plasminogen activator antigen (right) in plasma of patients with coronary artery disease and controls. Means (and SD) are shown.

Comment

Our findings suggest that the fibrinolytic system is altered in patients with coronary artery disease. In particular, the functional levels of the fast acting inhibitor of plasminogen activator are significantly increased. The observations that the overall euglobulin fibrinolytic activity is similar in patients and controls and does not correlate with the plasma plasminogen activator inhibitor activity are not totally surprising. The euglobulin fraction, indeed, contains other plasminogen activators different from tissue type plasminogen activator (and not neutralised by plasminogen activator inhibitor), which may represent more than 90% of the total activity and, most probably, do not have an important role in the activation of the fibrinolytic system in vivo.

The increased activity of plasminogen activator inhibitor in the plasma of patients with coronary artery disease may contribute to the impairment of the fibrinolytic capacity and thus represent another risk factor worthy of consideration in the disease.

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