Effect of oral gamolenic acid from evening primrose oil on menopausal flushing

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Abstract

***Objective*—To evaluate the efficacy of gamolenic acid provided by evening primrose oil in treating hot flushes and sweating associated with the menopause.**

***Design*—Randomised, double blind, placebo controlled study.**

***Setting*—District general hospital and teaching hospital.**

***Subjects*—56 menopausal women suffering hot flushes at least three times a day.**

***Intervention*—Four capsules twice a day of 500 mg evening primrose oil with 10 mg natural vitamin E or 500 mg liquid paraffin for six months.**

***Main outcome measures*—Change in the number of hot flushes or sweating episodes a month.**

***Results*—56 diaries were analysed, 28 from women taking gamolenic acid and 28 from those taking placebo. Only 18 women given gamolenic acid and 17 given placebo completed the trial. The mean (SE) improvement in the number of flushes in the last available treatment cycle compared with the control cycle was 1·9 (0·4) ($P < 0·001$) for daytime flushes and 0·7 (0·3) ($P < 0·05$) for night time flushes in women taking placebo; the corresponding values for women taking gamolenic acid were 0·5 (0·4) and 0·5 (0·3). In women taking gamolenic acid the only significant improvement was a reduction in the maximum number of night time flushes (1·4 (0·6); $P < 0·05$).**

***Conclusion*—Gamolenic acid offers no benefit over placebo in treating menopausal flushing.**

Introduction

The climacteric is characterised by a variety of distressing subjective symptoms, the most disruptive being the episodic vasomotor symptoms of hot flushes and sweating, which are experienced by 50% to 70% of women.[1] Although the exact cause of these symptoms is not known, several theories have been suggested, including oestrogen deficiency,[2] alteration in the hypothalamic thermoregulatory centre,[3] and changes in the peripheral and central mechanisms dependent on prostaglandins that stimulate the release of gonadotrophins through the hypothalamus.[4,5]

Currently, hormonal preparations containing oestradiol or conjugated oestrogens are widely used and considered to be an effective and well tolerated form of treatment for climacteric vasomotor symptoms. Little attention, however, has been paid to the management of menopausal flushing in women who cannot or do not wish to have hormone replacement therapy. Claims have been made for various drugs including clonidine, β blockers, and veralipride, but despite supportive data, beneficial results are rarely seen with these agents in clinical practice.[6,7]

Although neither clinicians nor the pharmaceutical industry have ever promoted evening primrose oil for the purpose, there is a current view among the lay public that it is effective in the control of menopausal vasomotor symptoms. Anecdotal cases have been reported supporting this in some menopausal women taking preparations of evening primrose oil. Consequently, large quantities of the oil in various formulations are being bought over the counter. In view of the possible theoretical benefits of the oil and the fact that it is being widely used by women in the general population its efficacy in suppressing adverse climacteric symptoms needs to be formally assessed.

There is no good scientific rationale yet for the use of this preparation in treating hot flushes. In animals prostaglandins induce the release of gonadotrophins through the hypothalamus and prostaglandin E_2 implants increase the release of follicle stimulating hormone.[5] Evening primrose oil contains gamolenic acid, a precursor of prostaglandin E_1, and is therefore thought to be unable to improve vasomotor symptoms. We evaluated the effect of the oil on hot flushes and sweating in a randomised, double blind, placebo controlled pilot study.

Subject and methods

Fifty six patients were recruited from the general gynaecology clinics of the North Staffordshire Hospital Centre, Stoke on Trent, and the Royal Free Hospital, London; from general practitioners' surgeries, and by self referral of volunteers. Before entering the trial they were informed that a non-hormonal preparation containing evening primrose oil was to be compared with a placebo in a blinded study designed to assess the benefits of evening primrose oil in treating menopausal flushes. It was explained that, although "folklore" ascribed great benefits to the use of evening primrose oil, there was no scientific evidence to support this belief. Possible side effects of the oil such as nausea and diarrhoea were also pointed out.

Patients included for study were menopausal women who had hot flushes at least three times a day and who had raised gonadotrophin (follicle stimulating hormone and luteinising hormone) concentrations or had had amenorrhoea for at least six months, or both. None of these women had received oestrogen replacement therapy or essential fatty acid supplements in the previous two months. Women taking any form of oestrogen replacement or other drugs for menopausal symptoms were excluded from the study, as were those requiring concurrent treatment with systemic steroids, non-steroidal anti-inflammatory agents, anticonvulsants, clonidine, and phenothiazides. The sample size was chosen to give a 90% chance of detecting a 13% change in the mean number of daytime flushes when testing at the 5% level of significance.

The study was conducted over 17 months at the two hospitals. Approval was obtained from the ethical committees. Women gave written informed consent before entry to the study.

During the first month of the study the women did not receive any treatment, in order to establish baseline values and to ensure correct daily documentation of self assessments in the diary cards provided. This was followed by random allocation to six months of treatment with active or placebo capsules, four being taken twice a day. Each gelatin capsule contained 500 mg evening primrose oil with 10 mg natural vitamin E (Scotia 05027) or 500 mg liquid paraffin. Liquid

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paraffin was chosen as the placebo because it is truly inert and is not metabolised or incorporated into cell membranes. The dose used was not expected to have any clinical effects on menopausal flushes or other symptoms of the menopause.

Patients were seen at entry for baseline measurements and assessments and thereafter at months 1, 4, and 7. Baseline assessments included a medical history and a blood sample to assay gonadotrophin concentrations. The number and severity of flushing and sweating episodes (day and night) were documented daily on the diary cards, as well as details of any adverse effects. The change in the number of daytime and night time episodes of flushing and sweating between the initial control cycle and the last available treatment cycle was calculated for each subject. The significance of the improvement was assessed by the Wilcoxon signed ranks test. Differences between groups were assessed by the Mann-Whitney U test.

Results

We analysed 56 diaries, 28 from women taking gamolenic acid and 28 from those taking placebo. All data were included in the analysis irrespective of any lack of compliance or protocol violation—that is, the analysis was conducted on an intention to treat basis. Eighteen women given gamolenic acid and 17 given placebo completed the trial.

The two groups were similar at baseline (table I).

TABLE I—*Baseline characteristics of patients randomised to receive gamolenic acid or placebo. Values are means (SDs or ranges) unless stated otherwise*

Characteristic	Gamolenic acid (n=25*)	Placebo n=28)
Age (years)	53·7 (45-62)	54·2 (46-67)
Parity	1·24 (0-3)	2·18 (0-6)
No of flushes:		
Daytime	4·51 (1·86)	5·21 (2·84)
Night time	2·72 (1·95)	2·39 (1·34)
Duration of symptoms (years)	4·6 (1-24)	4·6 (1-17)
Previous treatment (No of patients):		
Hormone replacement therapy	7	4
Essential fatty acids	1	0
Clonidine	0	1
No of patients in whom prostaglandin E_2 contraindicated	6	1

*Data missing on three patients.

Table II shows the improvement in the number of episodes of flushing or sweating between the control cycle and the last available treatment cycle.

All women given placebo showed a significant positive difference between control cycle and last cycle ($P<0·05$). Women given gamolenic acid, however, did not show a significant improvement between the control cycle and last available treatment cycle except for a reduction in the maximum number of night time flushes ($P=0·014$). However, whether this is a true difference or chance improvement remains uncertain.

TABLE II—*Improvements between control cycle and last available cycle and difference between improvements for women taking gamolenic acid or placebo*

	Gamolenic acid		Placbo		
	No of patients	Mean (SE) improvement	No of patients	Mean (SE) improvement between cycles	Difference in improvement between groups†
Mean No of flushes:					
Daytime	26	0·5 (0·4)	28	1·9 (0·4)***	−1·5 (0·6)
Night time	25	0·5 (0·3)	27	0·7 (0·3)*	−0·2 (0·4)
Maximum No of flushes:					
Daytime	26	1·6 (0·8)	28	4·0 (0·7)***	−2·4 (1·1)*
Night time	25	1·4 (0·6)*	27	1·0 (0·6)*	0·4 (0·8)
Mean overall severity	26	2·0 (3·7)	25	6·0 (2·4)**	−4·1 (4·5)

*$P<0·05$, **$P<0·01$, ***$P<0·001$ by Wilcoxon signed ranks test for mean improvement and Mann Whitney U test for difference between groups.
†Gamolenic acid−placebo.

All patients tended to show improvement, but because of the small number of patients a change in the mean number of daytime flushes of less than 13% cannot be detected. When improvements in the last available treatment cycle over control cycle were compared between treatments there was a definite trend in favour of placebo. However, there was no significant difference between treatments except for the maximum and mean numbers of daytime flushes ($P=0·02$).

Side effects noted during the study were minimal. Slight nausea was reported by three women taking gamolenic acid, but this was relieved when the drug was taken after meals only. Two patients taking placebo complained of dyspepsia and diarrhoea, probably due to the liquid paraffin used in the placebo preparation. They were withdrawn from the study at 3 and 4 months respectively. In all, 21 women did not complete the trial, and in every case withdrawal was because of a poor clinical response to the treatment.

Discussion

Vasomotor disturbances are the most characteristic symptoms experienced during the climacteric. Not all perimenopausal women, however, experience hot flushes or sweating. The prevalence of these symptoms is subject to wide cultural differences, being appreciably higher in Western women than in women from developing countries, where the menopause generally seems to be associated with fewer complaints.[8,9] In Europe and North America over 80% of women experience flushing at some time during the perimenopause (A Oldenhave, sixth international congress on the menopause, Bangkok, 1990), and many seek treatment for this.

Flushing and sweating are considered the most noticeable effects of falling concentrations or lack of oestrogen, and they usually disappear once the low oestrogen concentration is stabilised. As oestrogen deprivation is at least in part responsible for vasomotor symptoms at the climacteric, hormone replacement seems to be the most logical treatment.[10]

Hormone replacement therapy has now been available for over 30 years, and its use is growing. Debate about the safety of hormone substitution is also increasing. Although extensive studies on the subject have shown the benefits to far outweigh the risks, women and their doctors remain concerned about the side effects of hormone replacement and many avoid such treatment whenever possible. Though this fear is unwarranted in most women, oestrogen is contraindicated for a few women who have symptoms. Nonhormonal treatments such a clonidine, β blockers, and veralipride have been used in such cases, but controlled studies have shown oestrogen to be superior.[6,7,11]

Lately, women averse to using hormones have resorted to taking preparations of evening primrose oil, which they consider to be safe and effective in controlling the symptoms of a natural aging process. The active ingredient responsible for these beneficial effects is believed to be gamolenic acid, the immediate metabolite of linoleic acid.

Linoleic acid is an essential fatty acid found in a wide variety of foods. Particularly concentrated amounts are found in plant seed oils, of which evening primrose oil is the most desirable source for several reasons. Not only does evening primrose oil have up to 10% of its fatty acids as stable gamolenic acid but also it is devoid of the saturated fatty acids and n-3 fatty acids which interfere with the metabolism and biological activity of gamolenic acid.

The results from our pilot study show that gamolenic acid provided by evening primrose oil, although popularly believed to alleviate vasomotor symptoms of the menopause, offers no benefit over placebo. This

Clinical implications

- Over 50% of menopausal women suffer from distressing vasomotor symptoms, whose exact cause remains unclear
- Oestrogen replacement is effective treatment for most women, but effective non-hormonal alternatives are required for those averse to taking oestrogen or in whom oestrogen is contraindicated
- Evening primrose oil is a rich source of gamolenic acid, popularly believed to suppress menopausal flushing
- This study showed that evening primrose oil had no benefit over placebo in the alleviation of vasomotor symptoms
- Given these results and the lack of a scientific reason for using gamolenic acid, the use of evening primrose oil in treating menopausal flushing cannot be supported

may be because metabolites of evening primrose oil provide high concentrations of prostaglandins which decrease the affinity of ligands such as oestrogens and other hormones for their receptors.[12] In addition, several experiments have shown prostaglandins acting at the hypothalamus stimulate the release of follicle stimulating hormone and luteinising hormone.[5] High concentrations of these pituitary gonadotrophins have long been implicated in the production of menopausal vasomotor disorders, although the exact mechanism remains elusive. Based on the data from this small pilot study and on the lack of a hypothetical rationale for using gamolenic acid, we cannot support the use of evening primrose oil in the treatment of menopausal hot flushes. Larger studies are required.

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Risk of gynaecomastia associated with cimetidine, omeprazole, and other antiulcer drugs

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Abstract

***Objective*—To study the risk of gynaecomastia associated with cimetidine, misoprostol, omeprazole and ranitidine.**

***Design*—Open cohort study with nested case-control analysis.**

***Setting*—General practices in United Kingdom that had computerised offices, 1989-92.**

***Subjects*—81 535 men aged 25-84 years who received at least one prescription for cimetidine, misoprostol, omeprazole, or ranitidine during the study period.**

***Main outcome measures*—New occurrences of idiopathic gynaecomastia diagnosed by general practitioner.**

***Results*—The relative risk of gynaecomastia for current users of cimetidine compared with non-users was 7·2 (95% confidence interval 4·5 to 11·3). Relative risks for misoprostol, omeprazole, and ranitidine were 2·0 (0·1 to 10·7), 0·6 (0·1 to 3·3), and 1·5 (0·8 to 2·6), respectively. Current users of cimetidine on a daily dose ≥1000 mg had more than 40 times the risk of developing gynaecomastia than non-users. The period of highest risk was seven to 12 months after starting cimetidine treatment. Spironolactone (relative risk 9·3 (3·3 to 26·1)) and verapamil (9·7 (2·6 to 36·0)) were associated with a relative risk of gynaecomastia comparable to one for cimetidine.**

***Conclusions*—Use of cimetidine, but not the three other antiulcer drugs, is associated with a substantially greater risk of gynaecomastia in men. A strong dose-response relation was present among cimetidine users.**

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Introduction

Gynaecomastia (enlargement of true breast tissue as opposed to adipose tissue) was a common clinical finding in case series.[1-3] The differential diagnosis of gynaecomastia depends on physiological and pathological criteria, and pathological gynaecomastia can be further classified into that associated with other medical conditions and idiopathic gynaecomastia. Cimetidine has repeatedly been reported as causing gynaecomastia,[4-7] and ranitidine was associated with gynaecomastia in a single case.[8] More recently omeprazole, a proton pump inhibitor also used as an ulcer healing drug, has been associated in more than a dozen cases with the development of gynaecomastia.[9-11] No epidemiological study has been published comparing the incidence of gynaecomastia among the various ulcer healing drugs. We performed a large population based cohort study which provides estimates of the absolute and relative risk of idiopathic gynaecomastia in patients who received cimetidine, misoprostol, omeprazole, or ranitidine, four drugs used primarily for treating peptic ulcer disease. The results are based on information held on British general practitioners' computers.

Methods

Over four million residents in the United Kingdom are enrolled with selected general practitioners who use office computers provided by Value Added Medical Products (VAMP) Research and have agreed to provide data for research purposes. They record medical information in a standard manner and supply it