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A randomised controlled trial of medroxyprogesterone acetate in mastalgia

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A double-blind crossover study giving 20 mg/day of medroxyprogesterone acetate during the luteal phase was carried out in 26 women with cyclical mastalgia. Symptomatic response to this progestogen supplementation or placebo was assessed objectively by clinical examination and subjectively by linear analogue scales and breast pain charts. No significant relief of pain or tenderness was found on placebo or active treatment, irrespective of treatment order, and breast nodularity was similarly unaltered. No evidence of progesterone deficiency or prolactin abnormality was found. Side-effects were incurred in 11 patients (five on placebo, five on active treatment and one while on both) and were mostly vague premenstrual symptoms. We conclude that the therapeutic response of medroxyprogesterone acetate in cyclical mastalgia is no better than placebo and that progestogen supplementation can no longer be recommended for routine use in the management of breast pain.

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Mastalgia remains an under-reported *(1,2)* and poorly recognised condition *(3,4)*, but is the most frequent reason for breast consultations in general practice *(5)*. Patients with persistent severe breast pain, which has not responded to simple reassurance after the exclusion of breast cancer and which significantly affects life-style, warrant endocrine therapy.

No specific pathological features have been found to correlate with breast pain, but a useful clinical classification has been described *(6)*; cyclical and non-cyclical patterns of mastalgia being differentiated by taking a simple clinical history and using a breast pain chart. The cause of non-cyclical mastalgia remains obscure, but a hormonal aetiology would seem likely for cyclical mastalgia by virtue of its close temporal relationship to the menstrual cycle and response to hormonal treatment, which has been established with several controlled trials *(7–9)*. No consistent abnormality in ovarian function has been described in cyclical mastalgia *(10)*, but hypothalamopituitary function may be disordered *(11)*.

Mauvais-Jarvis and coworkers have suggested the hypothesis that women with benign breast disease (including mastodynia, another term for mastalgia) have a low progesterone output by the corpus luteum, producing relatively unopposed oestrogen activity *(12)*. They also postulate that progestogen supplementation should correct this 'relative hyper-oestrogenism', and alleviate

the condition *(13)*. Their open study is supported by a controlled trial using lynestrenol for the treatment of mastodynia but thermography, a poorly defined parameter, was used to assess response *(14)*.

However, several workers have failed to find evidence of lowered serum progesterone during the luteal phase in benign breast disease *(15–17)* and cyclical mastalgia *(18, 19)*. Hence, there is currently much controversy over the place of progestogen supplementation in the treatment of cyclical mastalgia. It was the aim of this study to establish the efficacy of progestogen supplementation with medroxyprogesterone acetate and to investigate luteal serum sex steroid levels both on and off treatment.

Patients and methods

A series of 26 women with pronounced cyclical mastalgia (CM) of at least 6 months duration were entered into the trial. The patients were referred from the breast clinic, or via another surgeon for treatment of their breast pain. Each was examined clinically and breast cancer was excluded with mammography and fine needle aspiration cytology as required. Concurrent hormonal therapy was not permitted, but patients on prior hormonal therapy were admitted if there was a 2 month 'wash-out' period before the pretrial observation.

Trial design

The trial was carried out in the mastalgia clinic at the University Hospital of Wales, Cardiff and Ninewells Hospital, Dundee. Informed consent was obtained from each patient. A double-blind crossover structure was used giving therapy for a total of 6 months after an observation period of at least 2 months (Fig. 1). Following the observation period, patients with persistent symptoms were randomised to receive either placebo or 20 mg medroxyprogesterone acetate (MPA) per day from day 10 to 26 of the menstrual cycle with crossover to the alternative therapy after 3 months. Patient compliance was aided using a tablet calendar box (Fig. 2) with identical placebo tablets. The treatment order was randomised and the code was held by the hospital pharmacist and broken only when a patient completed or withdrew from the trial.

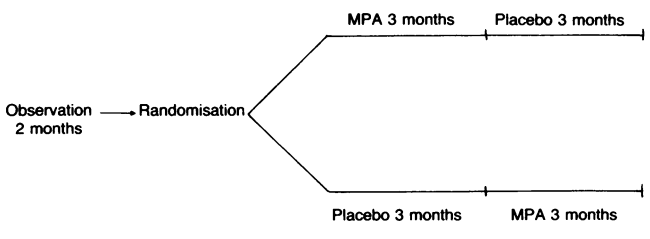

Figure 1. Trial design.

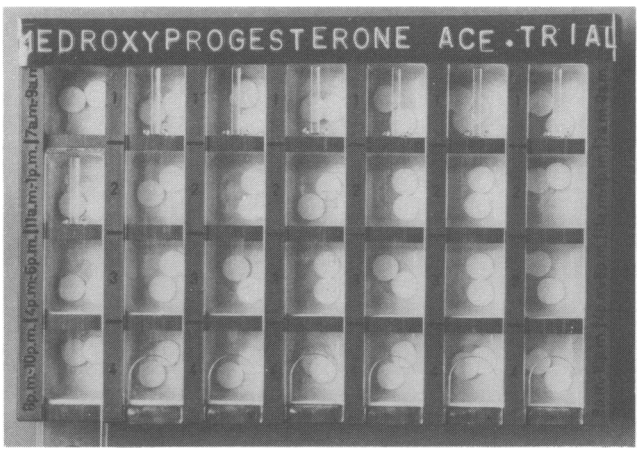

Figure 2. Tablet calendar box. Starting at the top left-hand corner and working across the box, patients were asked to empty a space (containing 2 × 10 mg MPA or identical placebo tablets) per day for weeks 1–4; ignoring the times along the sides of the box, which were used for another study.

Assessment

Each patient was examined late in each menstrual cycle and breast tenderness and nodularity were recorded using a simple numerical scale (1 = none present, 2 = some, 3 = marked). Clinical response was similarly assessed (1 = asymptomatic, 2 = some improvement, 3 = no improvement, 4 = worse). The patient's subjective response was assessed using a 10 cm linear analogue scale *(20)*, which was completed at each clinic visit. These were completed by the patient without supervision in a separate room. Subjective response was also monitored using the Cardiff Breast Pain Chart *(21)*, and expressed as a percentage of maximum days attainable for total and severe days of pain to allow for variation in cycle length.

Specific enquiry into side-effects was made at each clinic visit and weight and menstrual regularity recorded. Patient compliance was also documented by the pharmacist.

At each visit, 10 ml of clotted blood was taken for future assay of hormone levels. Blood samples were drawn from an antecubital vein and centrifuged at 4°C and the serum separated within 2 h of venepuncture. All serum samples were stored at −20°C until the completion of the study, when they were batch assayed for sex steroid hormone levels by radioimmunoassay at the Tenovus Institute *(22)*.

Serum prolactin was determined using an automated two-site immunoradiometric assay using human prolactin antibody and standard (Boots Celltech®) calibrated against International Reference Preparation 83/562 supplied by the National Biological Standards Board. The working range of the assay was 50–6500 mU/l with a coefficient of variation of <10%. Assay sensitivity was 50 mU/l.

Table I. Clinical assessment of tenderness, nodularity and response

	Clinicans' scores (mean ± SD)		
	Tenderness	*Nodularity*	*Response*
MPA—first group ($n=9$)			
Pretrial	2.0±0.5	2.1±0.6	—
End of MPA	1.7±0.7	1.7±0.7	2.6±0.5
End of placebo	1.9±0.8	1.7±0.7	2.3±1.0
Placebo—first group ($n=9$)			
Pretrial	2.0±0.7	1.7±0.9	—
End of placebo	1.9±0.8	1.2±0.7	2.8±1.0
End of MPA	2.1±0.9	1.3±0.7	2.8±1.2

End of MPA scores *vs* pretrial or post-placebo P = NS (Wilcoxon signed rank test)

Statistical analysis

Wilcoxon's signed rank tests were used to analyse the subjective linear analogue and breast pain chart data recorded at the pretrial, 3-month and 6-month periods. The means of the clinician's assessments of tenderness, nodularity and response were also compared by the Wilcoxon signed rank test. Student's t test was used to analyse the total differences in observations (irrespective of treatment order) for both the linear analogue and breast pain chart scores after 3 months' treatment with placebo or MPA. Serum sex steroid hormone levels were compared using the Wilcoxon's signed rank test for collective paired data and the Mann–Whitney U test for unpaired data.

Results

The mean age at presentation was 35.0 years (range 25–45 years) and the mean duration of mastalgia was 3.8 years (range 1–11 years). Eight patients dropped out during the 6 months of treatment; four due to lack of efficacy on placebo, one due to side-effects (also on placebo), one became pregnant on active therapy (and was delivered of a normal healthy baby) and two patients were non-compliant. The overall drop-out rate was 15%. This, therefore, left 18 patients who completed the full 6 months (9 in the placebo first group and 9 in the MPA first group). Due to a freezer breakdown, hormone levels for the patients in the first half of the study were lost and therefore complete paired hormone data is available for only seven patients.

Analysis of the clinical assessment for the remaining 18 patients showed no significant relief of tenderness, nodularity or response on placebo or MPA, irrespective of treatment order (Table I). Similarly, the linear analogue data (displayed graphically as means in Figs. 3 and 4) showed no significant relief of pain or tenderness, when pretrial scores were compared with the paired 3-month scores on placebo or MPA, or when end of treatment scores were compared for each treatment group. When the data were also analysed collectively comparing the total end of treatment period scores on placebo or MPA for both groups together, no significant difference was found for the linear analogue score of pain and tenderness or the clinical assessment of tenderness, nodularity and response using the matched pairs Student's t test. Breast pain chart analysis, which may more closely reflect the overall temporal change in breast pain for the patient, also revealed no significant difference between pretrial and end of treatment scores for both total and severe pain, irrespective of treatment order (Fig. 5). There was also no significant difference between scores at the end of treatment with placebo or MPA whether the data were analysed separately in the two groups or collectively analysing the total paired differences in observations for all patients.

Before carrying out this study we sought statistical advice and calculated that for a significance for the test of $P<0.05$, with a standardised difference of 1.3 (based on previous effective treatments for mastalgia studied in our clinic which give a 50% or more reduction in symptoms), 17 patients were required to give a power of over 80% for the study. As the combined data (irrespective of treatment order) is from 18 patients who are their own

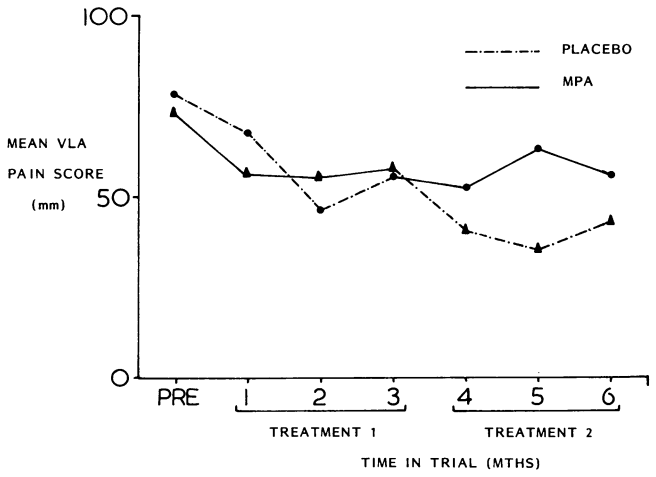

Figure 3. Mean luteal linear analogue scores for each group for breast pain.

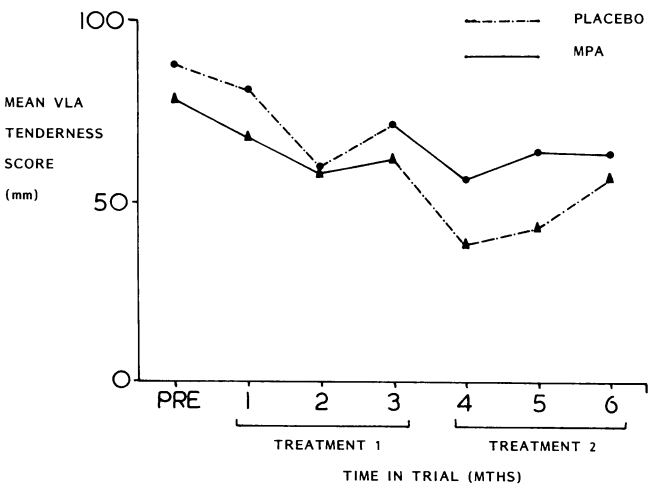

Figure 4. Mean luteal linear analogue scores for each group for breast tenderness.

controls, the total number of observations is 36, giving a corresponding power of 98% for a significance level of $P < 0.05$ and we are therefore confident that a type II statistical error has not been made and that the null hypothesis is correct.

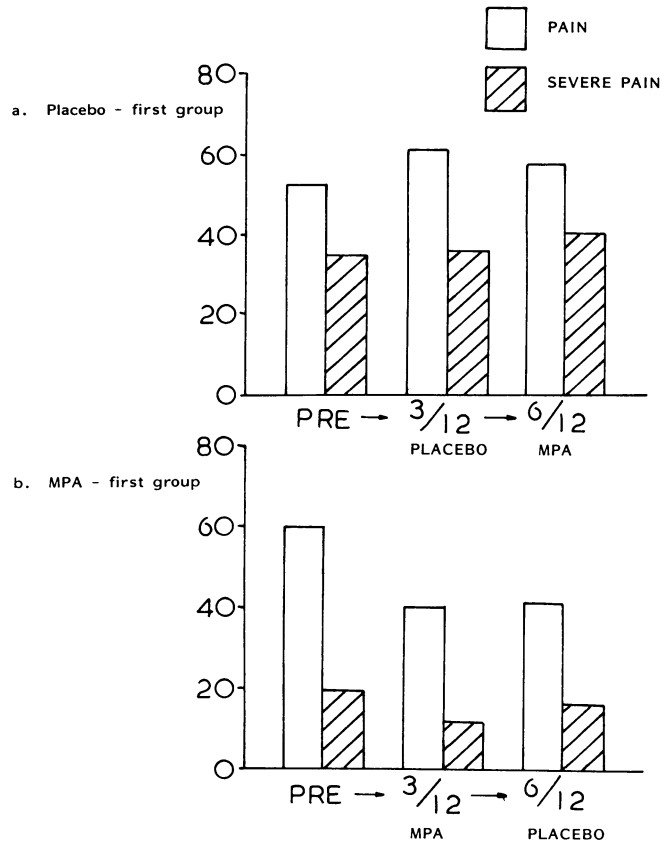

Figure 5. Mean breast pain chart scores for each group, expressed as a percentage of maximum days of pain attainable for the pretrial and end of treatment period months.

Table II. Paired luteal serum hormone levels at the pretrial and end of treatment periods, irrespective of treatment order

	Mean luteal hormone levels ± SD		
Period	*O (pM)*	*P (nM)*	*O/P ratio*
Pretrial	230± 88	22±16	23± 30
End of MPA	*203± 37	16±13	55±101
End of Placebo	*362±174	27±22	186±444

O = Oestradiol; P = Progesterone
End of MPA *vs* end of placebo or pretrial levels, P = NS (Wilcoxon signed rank test, $n = 7$) except: $*P = 0.022$

Pretrial luteal serum progesterone levels for paired patients were found to lie within the normal range (3–95 nM), and did not significantly rise after supplementation with MPA or on placebo (Table II). The mean levels of oestradiol were similarly within the normal range (180–1100 pM) for all paired patients before entry and did not significantly change during treatment, although there was a significant difference between end of treatment levels of oestradiol (serum oestradiol being significantly lower after treatment with MPA compared to placebo). However, all values were well within the normal biological range and there was no significant change in the oestrogen/progesterone ratio both on or off therapy. When the total unpaired data available for patients were analysed separately, no significant difference was found between pretrial and end of treatment levels (Table III). Also, normal basal levels of prolactin were found before, on and off therapy.

Side-effects occurred in 11 patients (five on placebo, five on MPA, and one while on both) and were mostly vague premenstrual symptoms.

Discussion

There is currently much controversy on the role of progestogens in the treatment of mastalgia. Mauvais-Jarvis and coworkers have reported low luteal progesterone levels in women with benign breast disease, which has led to the 'oestrogen window hypothesis' with a proposed 'hyperoestrogenism' in mastalgia *(12,13)*. They have therefore advocated that supplementation with a progestogen should ameliorate the condition. They gave a sequential administration of an oral progestogen (lynestrenol, 10 mg/day for 15 days/cycle) together with a novel topical application of progesterone given daily to the overlying skin of the breast. They reported a spectacular improvement in mastodynia (96%) and nodularity (85%) along with the correction of the systemic (and presumed local) hormonal insufficiency which lends biological plausibility to the hypothesis. Their findings were also echoed by Colin *et al. (14)* who reported a useful improvement in mastodynia using the same dosage of lynestrenol in a double-blind trial, but the unreliable

Table III. Unpaired luteal serum hormone levels at the pretrial and end of treatment periods

Period	*Number in Group (except where indicated)*	*Mean luteal hormone levels±SD*			
		O (pM)	*P (nM)*	*O/P ratio*	*PRL (mU/l)*
Pretrial	17	263±114	*24±13	17± 20	209±209 ($n=14$)
End of MPA	11	†198±106	*13±13	54± 83	181± 78 ($n=10$)
End of placebo	9	†372±174	26±20	149±392	144± 42 ($n=7$)

(O = Oestradiol; P = Progesterone; PRL = Prolactin)
End of MPA *vs* end of placebo or pretrial levels P = NS
(Mann–Whitney U test) except: *$P=0.0305$, †$P=0.0062$

parameter of thermography was used to assess response. However, he also reported lowered luteal progesterone levels relative to a control group.

Evidence of this inadequate corpus luteum function in mastalgia has not been found in a number of other studies examining women with benign breast disease *(15–17)* and cyclical mastalgia *(17,18)*. In this study we have found that the therapeutic response of MPA in cyclical mastalgia is no better than placebo, and that sex steroid hormone levels lie within the normal range in the luteal phase and do not alter significantly on both placebo or MPA. The conflicting findings between these reports (including the present study) and those of Mauvais-Jarvis *et al. (13)* and Colin *et al. (14)* are difficult to explain. However, part of the controversy may be due to sampling error, infrequent sampling in the luteal phase or cross-reactivity in the assay system. England *et al. (16)* used daily blood sampling with reference to the mid-cycle luteinising hormone peak and Walsh *et al. (18)* dated blood samples with reference to the onset of menstruation subsequent to venepuncture. The progesterone profiles for these two groups have been similar. Mauvais-Jarvis *et al. (13)*, however, used the 'thermal plateau' as the reference point for each blood sample, which is an unreliable method for determining the start of the luteal phase *(23)*. Furthermore, erroneous clinical and hormonal data may also stem from the imprecise definitions previously used for benign breast disorders, which have now been classified into more homogeneous subgroups *(24)*.

This present study has examined the hormonal background in a well-defined group of women with cyclical mastalgia and has shown, in concordance with our previous findings of daily salivary progesterone levels in the luteal phase *(19)*, no evidence of luteal progesterone deficiency or change in sex hormone levels on or off treatment with progestogen supplementation. This evidence therefore does not support the hypothesis of 'relative hyperoestrogenism' in cyclical mastalgia, despite the fact that a hormonal aetiology is strongly suspected for this condition in view of the previous natural history studies and hormonal investigations *(11,25)*. We have also found that the therapeutic response of MPA in cyclical mastalgia is no better than placebo, and therefore advise that progestogen supplementation can no longer be recommended for routine use in the management of breast pain.

We are indebted to Mrs Edna Lewis who has voluntarily given her services to the mastalgia clinic over the past 15 years. We also wish to acknowledge help in statistical analysis from Dr T Peters, University Department of Medical Statistics, Cardiff and Mr J Melhuish.

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Granuflex dressings for closed surgical wounds combined with suction drainage

When skin flaps are raised during surgery closure is often combined with suction drainage, but if the wound allows any air leaks suction is ineffective and haematoma formation ensues. Conventional dressings do not always provide a reliable seal for the wound.

Granuflex® flexible dressings* are recommended for open wounds, but they can be advantageous for closed wounds where suction drainage is used to obliterate tissue spaces. The hydrocolloid component of the dressing reacts with wound exudate to form a gel which effectively seals the wound against air leaks. Strips of Granuflex, 2–4 cm in width, can be applied to a wound and, as the dressing is flexible, it is particularly useful for irregular wounds with awkward configurations.

Over the last 3 years, Granuflex dressings have been applied following 33 mastectomies and 22 parotidectomies in combination with suction drainage. Two cases in each group developed a haematoma, on two occasions due to inadvertent early drain removal, but in no instance was this associated with a loss of the vacuum in the drain.

The adaptation of Granuflex dressings for closed surgical wounds has, in our practice, improved the effectiveness of suction drainage. Its main advantage has been its gentle adherence and its effectiveness in producing a wound seal whilst its flexibility makes it ideal for irregular wound contours. In addition, because of the gel formed beneath Granuflex, it has proved a kind dressing and can be recommended for wounds following operations such as circumcision, where the dressing will adhere satisfactorily but can be removed with little pain.

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