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Short report

Treatment of menstrual migraine by oestradiol implants

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SUMMARY The suppression of cyclical ovarian activity and the creation of constant oestradiol levels in blood by subcutaneous oestradiol implants has been used to treat 24 patients with menstrual migraine for up to five years. Twenty-three patients improved with treatment, 20 (83%) became completely or almost completely headache-free. Regular monthly periods were induced with cyclical oral progestogens. The treatment was not associated with any problems. The results support the concept that oestrogen withdrawal in the late luteal and menstrual phases of the ovarian cycle is the important precipitating factor in menstrual migraine, and such attacks can be prevented by suppressing the hormonal fluctuations associated with the ovarian cycle.

Migraine occurs in approximately 19% of women.[1] In a significant number the migraine headaches appear to be influenced by hormone changes associated with the ovarian cycle, in that attacks usually commence after puberty, and in up to 60% the headaches are related to menstruation.[2] Pregnancy is associated with total or partial cessation of attacks and the combined oral contraceptive pill may precipitate migraine during the week off interval. These observations, and the lack of consistent differences in the plasma concentrations of the ovarian hormones between women suffering from menstrual migraine and controls,[3] has led to the concept of hormone withdrawal in the premenstrual phase as the causative factor. Somerville[4] believed that falling oestradiol levels, rather than progesterone were responsible, as he was able to abort menstrual migraine attacks by short-acting injections of oestradiol but not by progesterone. He also attempted prophylaxis using oral and injectable oestragens but failed to maintain adequate plasma oestradiol level and did not influence the frequency of migraine attacks. We report our experience of the treatment of menstrual migraine by subcutaneous implants of oestradiol. Oestradiol implants are already established in treating the symptoms of the climacteric,[5] and it was considered that a dose large enough to suppress ovulation[6] and the biochemical changes of the ovarian cycle would prevent menstrual migraine attacks by producing constant oestradiol levels for a period of six months.[7]

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Patients and method

Over the past five years 24 patients have been treated with subcutaneous oestradiol implants (Organon Laboratories) for menstrual migraine. The diagnosis of migraine fulfilled the definitions layed down by the World Federation of Neurology's Research Group on Migraine and Headache. All patients had tried prophylactic drug therapy and were referred by general practitioners or neurologists for hormone treatment because of failure to maintain adequate relief and reduction in the number of attacks of migraine.

Characteristics of the Study Group Of the 24 patients, five had classical migraine and 19 common migraine. All patients complained of regular attacks immediately before or during menstruation for an average of 23·3 years (range 2–37). Twenty-one first developed migraine during or within a few years of puberty, and all 20 of the parous patients noted improvement during pregnancy. Eight of the 12 patients who had taken oral contraception found it made their migraine worse, and 16 women also suffered from the premenstrual syndrome.

Oestradiol Implant Treatment The average age at the start of implant treatment was 40·6 years (range 32–51), with 2·5 years (range 0·5–5) being the mean duration of treatment at a starting dose of 100 mg of oestradiol, the dose that has been shown to inhibit ovulation and be effec-

tive as a contraceptive.[6] Subsequent doses were generally decreased to a maintenance of 50 mg, and were repeated at an average interval of 6·2 months (range 4–7), at the time when the effect of the implant was wearing off and symptoms were beginning to reappear. On average each patient had 4·9 implants (range 1–9), of which 41% were 100 mg, 1% were 75 mg, and 58% were 50 mg of oestradiol. The implants were inserted into the subcutaneous fat of the lower abdominal wall according to the method described by Thom and Studd.[8] Patients were also given cyclical progestogen (Norethisterone 5 mg daily for 7 days per month) to induce regular endometrial shedding and prevent the development of endometrial pathology.[9] The contraceptive effect of the treatment was explained to all patients, who were advised to use non-hormonal methods of birth-control during the first three months of the first implant.

Results

All but one patient noted an improvement in their menstrual migraine following treatment. Eleven (46%) became completely headache-free and nine (37·5%) gained almost complete symptomatic relief. All these patients were able to reduce or stop previous therapy and considered the implant treatment to be the most effective. Three patients (12·5%) reported partial relief, and one patient (4%) gained no benefit. The monthly course of progestogen produced regular withdrawal periods in all patients. Periods were usually lighter and less painful than before treatment, although four women complained of heavier blood loss. No other problems were associated with the treatment. Nineteen patients continue to have treatment with oestradiol implants. The remainder stopped either because of concern over long-term hormone therapy, or because of the inconvenience of travelling to a clinic a long way from home. One patient stopped after one implant because there was no improvement of symptoms.

Discussion

Treatment with subcutaneous oestradiol implants produced a response rate of 96% in patients with menstrual migraine in whom prophylactic drug therapy had failed. This effect is considerably greater than any possible placebo response. Our results support the concept that oestrogen withdrawal is the important precipitating factor in this condition, and show that suppression of ovulation and prevention of the biochemical changes associated with the ovarian cycle by increasing plasma oestradiol concentrations is an effective therapy. A similar effect might be achieved by taking the combined oral contraceptive pill continuously and will be appropriate for the younger women. However, in general, implants are preferable to continuous oral contraceptive therapy as percutaneous oestradiol is associated with fewer side effects than synthetic oestrogens and progestogens, can be safely used in an older age group, and is particularly useful if such patients are approaching the menopause. Implants also produce more physiological plasma concentrations of oestradiol and oestrone than follows administration of any oral oestrogens. Although Somerville used oestradiol implants in four cases of menstrual migraine, his biochemical data showed considerable variability in plasma levels of oestradiol achieved. Previous studies in our clinic using oestradiol implants in post-menopausal women showed a sustained elevation of oestradiol to a mean of 600 pmol/l and a mean plasma oestrone concentration of up to 360 pmol/l for six months following implantation which corresponds with the mean duration of effectiveness of an implant in our study.

The mechanism of action of oestradiol withdrawal in the genesis of menstrual migraine is not known. Oestrogens may cause arterioles to hypertrophy in headache-susceptible women, as shown in the endometrium by Grant.[10] The uterine arterioles are known to constrict in the immediate premenstrual phase, and this has been shown to be related to oestrogen withdrawal.[11] Such a mechanism if applied to cranial vessels may explain the phase of vasoconstriction during a migraine attack. Oestrogens are also known to influence the metabolism of serotonin and platelet aggregation, both of which have been implicated in the pathogenesis of migraine.[12 13]

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