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Medroxyprogesterone Acetate for Treatment of Migraine in Females

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ABSTRACT

Objective Estrogen deficiency has always been regarded as an important precipitating factor in menstrual migraine. We propose that endocrinological fluctuation, rather than a lack of estrogens, is the major causal factor in female migraine.

Design Randomized placebo-controlled study.

Setting Selected subjects were attending at the endocrinological out-patient department of Vienna general hospital.

Subjects 235 healthy, hysterectomized women aged between 18 and 65 years with a diagnosis of migraine were included in the study.

Intervention 155 patients (group A) medroxyprogesterone acetate (MPA) and 80 patients (group B) were given monthly injections of MPA and placebo, respectively, from the beginning of the study.

Results A complete elimination of migraine attacks was achieved in 63% in group A and in 14% in group B ($p<0.001$).

Conclusion Our findings are in contrast to results suggesting that low estradiol in the luteal phase is responsible for migraine attacks. These may rather be caused by endocrinological fluctuations as they can also be blocked by a continuous delivery of steroids such as estradiol implants, percutaneous estradiol and MPA.

Key words : medroxyprogesterone acetate, menstrual migraine, gonadotropin fluctuation

Researches on the health of women, which are expanding fundamental biological and clinical knowledge, will have a positive effect on global morbidity and mortality patterns of women. These researches seek to better understand conditions that are unique to women as well as those that affect both sexes. Learning whether and when differences exist between genders and understanding their potential health implications should influence policies to improve the health status of both women and men.[1]

Migraine may affect up to 15% of the population at some time in their life. Women are affected three

times more often men.[2] Sixty percent of female migraine patients describe a connection of symptoms to the menstrual period.[3,4] Therefore migraine has been considered not only a manifestation of both neuroregulation and endocrinological dysfunction.[5,6]

Hormones influence brain function from gestation through life. Estrogen enhances, and progesterone diminishes, neuronal excitability experimentally. Hormonal effects of the CNS also depend on the region of the brain on which the hormone acts.[7] Extensive experimental data show that progestins exert an inhibitory effect on neurons. Acting like barbiturates and benzodiazepines, progesterone metabolites in low concentrations modify gamma-aminobutyric acid-(GABA) A-receptor agonist binding and potentate GABA-induced chloride currents.[8] This information is relevant to understanding the mechanisms of migraine and to developing a more effective treatment.

Current therapies are either prophylactic, such as b-blockers, calcium channel blockers, methysergide, or acute, such as analgesics, non-steroidal anti-inflammatory agents, ergot derivatives or narcotics. Such therapies are often unsatisfactory because of their low efficacy and unacceptable side-effects. The aim of our study was to clarify and evaluate a still anecdottal observation. Migraine attacks being known to be associated with to vascular sensations, some gynecologists avoid prescribing the oral contraception combination pill for migraine patients,[9] preferring medroxyprogesterone acetate (MPA) for ovulation suppression instead.[10] While patients receiving this treatment do not only enjoy the contraceptive effects, but also report a decrease in the intensity or frequency of migraine crises, MPA has not yet been considered for migraine treatment. We therefore analysed the therapeutic effect of medroxyprogesterone acetate in migraine patients in a prospective, randomized, placebo-controlled study.

Materials and Methods

Patients

Selected patients were attending the endocrinological out-patient department of Vienna general hospital.

Candidates for the study were 235 healthy, hysterectomized women aged between 18 and 65 years, with a diagnosis of migraine (with or without aura) according to the International Headache Society classification,[11] who had, for at least 1 year, experienced between one and six migraine attacks of moderate or severe intensity per month.

Ethics Committee approval was obtained where appropriate, and informed consent was obtained from each patient before entering the study. Patients were excluded if they had taken prophylactic medication within weeks of the start of the study, were hypertensive (resting diastolic blood pressure >95 mmHg), had ischaemic heart disease or had any medical condition (e.g. renal or hepatic impairment) that might interfere with the interpretation of the study results or if they had a current or recent history of drug abuse (including alcohol).

Study Plan

Patients attended the clinic for a pretreatment visit, during which demography and medical history, haematology, biochemical and hormonal parameters (estradiol (E2), gonadotropins (FSH, LH) and prolactin (HPRL), and ECG were recorded. Migraine symptoms were graded using rating scales for headache severity (3, severe; 2, moderate; 1, mild; 0, none). Migraine does not consist solely of headache. Other symptoms frequently associated with migraine include nausea, vomiting and photophobia and/or phonophobia. Each of these symptoms was, therefore, assessed as present or absent before and after treatment, and the change in incidence of each symptom was summarized and, where appropriate, analysed statistically.

Patients returned for follow-up visits to the clinic 4, 8 and 12 weeks after the supply of the medication. At each visit, they underwent a physical examination

including heart rate, blood pressure and ECG. A blood sample was taken for the analysis of hormone parameters.

The frequency of migraine attacks was registered by patients in a personal calender. 150 mg of medroxyprogesterone acetate (Depo Provera R, Fa. Upjohn) or a placebo (hydroxybenzoacidmethylester, hydroxybenoacidpropylester in a stabilised watery solution) injection was applied intramuscularly every four weeks. Simple randomisation was performed by the pharmacy using sealed envelopes. The medication was distributed by pharmacy. The MPA solution and the control solution were the same in colour, consistency and smell. In a group of 155 patients (group A), MPA was injected every four weeks. In 80 randomly selected patients (group B) only a placebo injection was given every four weeks for the first three months.

Statistical analysis

Data were analysed using SPSS software. A student's t-test was used to detect for significant differences between mean values. $P<0.05$ was regarded as statistically significant.

Results

A total of 235 patients, who treated an attack with the study were randomized medication. For the main clinical variables (mean age, migraine history), there were no significant differences between the treatment groups at study entry.

Improvement in Headache

Improvement in headache from grade 3 or 2 to grade 1 or 0 after 8 weeks was achieved by 77% of patients received medroxyprogesterone acetate compared with 26% of patients treated with placebo ($p<0.001$). Thirty-one percent of the medroxyprogesterone acetate group and 6% of the placebo group, respectively, were completely pain-free. After 12 weeks, 83% of all medroxyprogesterone acetate patients, as compared with 30% of the placebo-treated patients, reported headache relief ($p<0.001$). Of these patients, 63% and 14%, respectively, were pain-free.

Nausea, Vomiting, Photophobia/Phonophobia

The superiority of medroxyprogesterone acetate over placebo at reducing the incidence of nausea, vomiting and/or photophobia/phonophobia was clearly demonstrated. Prior to treatment, 92% of all patients experienced at least one of these symptoms, but after the first injection 76% of those who received medroxyprogesterone acetate were free of these symptoms, as compared with 30% of those who received placebo injections.

Hormone parameters

The mean serum hormone parameters are presented in Table 1.

Table 1. Mean (SD) of hormone parameters before and after treatment

	GROUP A (n=155)		GROUP B (n=80)	
	BEFORE MPA TREATMENT	AFTER MPA TREATMENT	BEFORE PLACEBO TREATMENT	AFTER PLACEBO TREATMENT
E_2 (pg/ml)	45 (27)	15 (11)*	52 (31)	73 (34)
LH (mU/ml)	11.5 (10.1)	1.5 (0.4)*	10.4 (15)	12.1 (17)
FSH (mU/ML)	6.7 (3.4)	3.1 (0.7)*	5.1 (4.2)	4.7 (3.9)
HPRL (ng/ml)	12.7 (6.5)	14.3 (6.7)	10.7 (5.2)	11.8 (4.9)

* $p < 0.05$

Discussion

The study was confirmed on hysterectomized patients in order to ensure that it was truly a blinded study. The high frequency of menstrual irregularity in MPA patients would likely have disclosed to these patients that they were receiving the active drug.

In our study, the majority (75%) of the patients had a history of migraine without aura, whereas 12% suffered attacks with aura and 13% had a history of both migraine types. The baseline demographics and migraine history were, thus, typical of the general migraine population.

The use of MPA has been shown to be a highly effective and well tolerated treatment. There was no evidence that MPA treatment causes changes in blood biochemistry, haematology, vital signs or ECG status. Our results are in contrast to the assessment of Somerville's[9] interpr etation that decreasing estradiol levels rather than progesterone are responsible for migraine attacks. This was confirmed by percutaneous estradiol applications where migraine attacks showed an improvement in numbers and severity.[10]

Another pathophysiological explanation must therefore be assumed. Percutaneously administered estradiol (like implants) induces a rapid decrease of gonadotropins and probably also of releasing hormones and neurotransmitters,[11,10] a phenomenon which can also be observed after medroxyprogesterone injection.

The continuos administration of estrogen suppresses the gonadotropins despite subnormal estradiol-serum concentrations; the low estradiol level in the serum cannot restore the postulated estrogen deficiency or induce by itself the gonadotropin suppression. This must be done by a continuous supply of estrogens, which interfere with the pulsatile action of the pituitary gland and perhaps also of the hypothalamus. Gonadotropin suppression and, therefore, the possible reduction of neurotransmitters also occur after the administration of medroxyprogesterone acetate. In high doses, it induces a down-regulation of neuroendocrinological fluctuations, and this may be an explanation for the therapeutic success of medroxyprogesterone acetate, despite the observation that the cyclical neuroendocrinological activity continued in a few women of MPA. Further research will show whether MPA leads to the same suppressive effect on the cephalic vascular network as in the endometrium. Other studies on the mechanism of migraine have focused on the dilatation and increased pulsation of the external carotid artery and its branches.[12, 13]

In the treatment of women with demonstrable pelvic congestion, medroxyprogesterone acetate causes venous contractions (show in venograms) that lead to a reduction in pelvic congestion, presumably due to an improved venous clearance.[14] This finding suggests that cephalic arteries play an important role in the etiopathogenesis of migraine based on the same effect found in the inner genital tract.

Another explanation might be that, as is known, progesterone may lead to a suppression of vasodilatation as a result of the inhibition of NO synthetase.[15, 16] While the etiology of migraine is known to be multifactorial, we were able to show that the hormonally dependent factor in migraine patients may be influenced positively with MPA. Further studies will be necessary to confirm the possible benefit of MPA in migraine patients.

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