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Treatment of seizures with medroxyprogesterone acetate: Preliminary report

Article abstract—Medroxyprogesterone acetate (MPA), a synthetic progesterone, was added to the antiepileptic drug regimen of 14 women who had uncontrolled seizures. Of the 11 women who developed amenorrhea, 7 reported fewer seizures during MPA therapy. Overall reductions in seizure frequency averaged 30% (n = 11), declining from a baseline 8.3 ± 5.8 seizures per month to 5.1 ± 4.1 seizures per month ($p = 0.02$). No serious side effects were encountered, but spotting was common. These preliminary data suggest further evaluation of MPA for catamenial seizures.

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Seizure frequency is affected by the menstrual cycle.[1] Backstrom[2] reported that seizure frequency increased in seven women during menstruation, when estrogen and progesterone levels were low, and decreased during the midluteal phase, when concentrations of progesterone were high. A secondary increase in seizure frequency was seen at the time of ovulation, when estrogen levels were high and progesterone levels were low. Seizures were also more frequent during anovulatory cycles, when progesterone levels remained very low. We found similar patterns in 17 women studied for 49 ovulatory cycles.[3] These data, coupled with earlier observations,[4,5] led to the conclusion that changes in estrogen and progesterone concentrations play a role in the occurrence of seizures. When the concentration of estrogen is high relative to progesterone, seizures increase. Conversely, when progesterone levels are elevated, seizure frequency decreases. In experimental animals, estrogens have convulsant and progestins have anticonvulsant activity.[6-8] Zimmerman et al[9] used synthetic progesterone to treat intractable seizures, and there was improvement.[9,10] We therefore evaluated synthetic progesterone therapy in a group of women with seizures that had been refractory to standard drug therapy.

Methods. Nineteen women with intractable epilepsy were evaluated for baseline seizure frequency for 3 to 5 months. This pretreatment period included weekly determinations of antiepileptic drugs and hormone levels to be certain that the usual menstrual cycling pattern was not affected and to ascertain compliance with drug intake. Fourteen women gave informed consent to enter the trial of treatment with synthetic medroxyprogesterone acetate (MPA) (Provera, Upjohn Co., Kalamazoo, MI) in addition to their usual antiepileptic drugs. Thirteen patients

had uncontrolled partial seizures, and 1 had frequent absence attacks. In all patients, detailed gynecologic examination excluded any contraindication to hormone therapy. Drug therapy was stabilized before the study and was not changed during the hormone therapy. The patients were first given MPA as 10-mg tablets, two to four times daily. Six patients who failed to develop amenorrhea on the pills later accepted parenteral depot administration of the drug; amenorrhea proved to be more likely after depot doses than after oral administration. Intramuscular MPA was given as 120- to 150-mg depot doses at 6- to 12-week intervals, depending on the time of breakthrough bleeding.

Patients made monthly clinic visits for review of seizure frequency and for analysis of serum concentrations of antiepileptic drugs, MPA, estrogen, and progesterone. Visits were timed for 21 to 25 days after onset of last menses to determine the presence or absence of ovulation by assaying progesterone concentration. Response to MPA was defined as cessation of menstrual cycling and progesterone levels of less than 5 ng/ml during the expected luteal stage of the cycle. Follow-up ranged from 3 to 24 months, with an average of 12 months for the group.

Antiepileptic drug determinations were done by EMIT enzyme immunoassay method (SYVA Company, Palo Alto, CA). Radioimmunoassays were used for analysis of estrogen (estradiol) (Pantex, Santa Monica, CA) and progesterone (Nuclear Medical Systems, Newport Beach, CA); MPA levels were analyzed by the Upjohn Company, using the method of Cornette et al.[11] Data were evaluated by Student's paired *t* test.

Table 1. Change in seizure frequency

Pre-MPA	MPA	%
5	3	40
19	6	68
13	13	0
5	5	0
2	2	0
16	12	25
7	2	71
3.5	1	71
11	7	36
1.8	1.6	11
7.5	3.5	53
*8.3 ± 5.8	*5.1 ± 4.1	39%

n = 11.
$p = 0.02$.
* Mean ± SD.

Table 2. MPA levels (ng/ml)

	Mean	Range
Oral patients	5.2	3-15
Oral controls*	—	5-30
IM patients	2.6	1-9
IM controls*	—	5-10

* Control MPA levels are from Cornette et al[11].

Results. In 11 of the 14 women, regular menstrual cycles ceased, with consistently low (≤ 1 ng/ml) levels of serum progesterone (table 1). Seizure frequency changed from means of 8.3 seizures monthly before treatment to 5.1 seizures per month on treatment, averaging 39% fewer seizures. Seven patients who showed definite improvement averaged 52% fewer seizures, ranging from 25 to 71% reduction. All patients with reduced seizure frequency had partial seizures. The single patient with absence attacks had no decrease in total number, but the pattern changed from a cluster just before and at the onset of menses to a random pattern throughout the cycle. One patient was excluded because she withdrew after 3 months for evaluation of benign breast cyst. Two patients who took only oral MPA continued to have regular menstrual periods and a rise in progesterone during the luteal phase, indicating a lack of significant effect of MPA on the reproductive cycle.

Antiepileptic drug levels were essentially unchanged in baseline and treatment periods. Minor variations were consistent with changes in time of sampling. MPA was found in serum in all the women, including the two who failed to develop amenorrhea. MPA serum levels were higher while women were receiving the hormone orally than after parenteral depot administration (table 2).

Side effects were limited to persistent menstrual spotting. This was sufficiently frequent and/or annoying to lead to discontinuation of treatment in some patients. A second effect was a delay of 3 to 12 months in resumption of regular menstrual cycling long after the final depot dose. Patients receiving only oral hormone therapy began regular menstrual cycling immediately after treatment was discontinued. After a year of amenorrhea, one patient became pregnant 1 month after she stopped taking MPA orally. She delivered a normal, healthy, full-term boy.

Discussion. We found that one-half of the patients who entered the program of treatment with MPA had a reduction in seizure frequency in a mean follow-up of 1 year. All 7 of these patients were among the 11 who developed amenorrhea on treatment. Improvement in seizure frequency was moderate, averaging a 50% reduction. These figures are not unlike the improvement reported in new drug trials for patients with intractable partial seizures.[12]

The explanation for the improvement in seizure control is conjectural. A random change in number of attacks seemed unlikely, because no patient became

worse. A placebo effect could not be excluded, although placebo effects are minimal in some studies of uncontrolled seizures.[12] In a controlled trial of MPA and placebo, amenorrhea would betray active treatment. Medroxyprogesterone may have a direct anticonvulsant effect, especially because progestins have antiepileptic properties.[6-8] An additional or alternative mechanism of action might be the inhibition of ovulation and the consequent absence of an ovulatory estrogen peak.

Patients treated with parenteral MPA were more likely to show a decrease in seizures than those on oral therapy, as observed by Zimmerman et al.[9] MPA levels were lower in patients taking parenteral depot therapy than in those receiving tablets.[13] The anticonvulsant effect and the ability to produce amenorrhea may be due to the sustained release of hormone, and the constant presence of some MPA may be more important than the cyclic peaks and rapid clearance associated with oral administration. In one controlled study,[14] there was no antiepileptic effect of norethisterone when tablets were given for 21 days and discontinued for 7 days, perhaps because of the 1-week interval when no progestins were administered. In addition, the oral contraceptives they tested were testosterone-derivative progestins rather than a hydroxyprogesterone derivative such as MPA, which has more antiepileptic properties.[8,9] Other progestins have more antiepileptic effect than MPA, which was used because it is available in both oral and parenteral forms, and because there has been extensive experience with the drug in treating gynecologic disorders, indicating that it is safe.[15]

MPA serum levels after either oral or parenteral administration were 30 to 70% lower than concentrations reported by Cornette et al[11] (table 2) for normal controls given comparable doses. The kinetics of MPA are probably affected by hepatic drug metabolic activity, ie, enhanced by concomitant administration of enzyme-inducing antiepileptic drugs. Rats pretreated with phenobarbital had more rapid disappearance of MPA from tissues than untreated controls,[16] and elimination of polar metabolites increased.

In our patients and others,[17] there was no effect of MPA on the steady-state levels of antiepileptic drugs, although MPA may induce drug metabolism and may affect its own metabolism and route of elimination.[18]

We saw few side effects, but the safety of administration of MPA could not be ascertained in such a small study. Most of our patients experienced some spotting, especially at the time of the expected menses and especially in the first few months in patients who ultimately developed amenorrhea. This recognized effect[19] is usually a nuisance rather than an important medical problem. Nonetheless, several patients discontinued treatment because they did not tolerate the irregular bleeding, particularly if there had been no clear benefit in seizure control. Another recognized effect of depot MPA is delayed return to menstrual cycling for up to a year. Like others,[15] we noted a lengthy interval (6 to 12 months) before return of menstruation in all patients after the last depot dose. Ortiz et al[20] concluded that ovulation can be suppressed for a year after a single 150-mg intramuscular dose of MPA. They found that follicle maturation returned with increasing estrogen levels only when MPA levels declined to 0.5 ng/ml; ovulation was delayed until levels fell below 0.1 ng/ml. They concluded that resumption of the ovarian cycle depends directly on residual MPA concentrations rather than on secondary recovery of the hypothalamus, pituitary, or ovary. MPA is thought to inhibit ovulation by preventing only the *cyclic* release of luteinizing hormone from the pituitary. The hypothalamic-pituitary-ovarian axis is maintained during MPA therapy.[21]

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Tinnitus from intracranial hypertension

Article abstract—Five patients had unilateral tinnitus from increased intracranial pressure of different etiologies. In each case, the tinnitus was produced by a venous bruit and could be decreased by Valsalva's maneuver, head turning to the ipsilateral side, or by light pressure over the ipsilateral jugular vein. Correction of the increased intracranial pressure obliterated the tinnitus. Turbulence, created as blood flows from the hypertensive intracranial portion into the low pressure of the jugular bulb, is proposed as the mechanism producing the tinnitus.

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Subjective tinnitus has been related to increased intracranial pressure,[1] cochlear disease,[2,3] labyrinthitis,[4] head trauma,[5] Paget's disease,[6] temporomandibular disease,[3] acoustic neuroma,[5,6] brainstem lesions,[5] and drug toxicity.[4,7] Objective tinnitus has been associated with increased intracranial pressure,[8,9] arteriovenous malformations,[5,6,10-12] racemose angiomas,[1,8,13] intracranial aneurysms,[1,13] glomus jugular tumors,[4,6] benign cervical venous hums,[14] stenotic arterial disease,[5,6] high cardiac output,[4,5] and palatal myoclonus.[15] In many cases of objective tinnitus, no cause is found.[8,15-17] Although both subjective and objective tinnitus have been associated with increased intracranial pressure, reported cases are few, and the relationship is not generally appreciated by physicians. The purpose of this report is to define the relationship clearly.

Case reports. Patient 1. A 32-year-old woman developed a loud pulsatile whistling noise in the right ear, which increased with inspiration or turning the head to the left. Conversely, the sound decreased during Valsalva's maneuver, on turning the head to the right, or, most effectively, with light pressure over the right side of the neck near the angle of the jaw. Four months prior to admission, skull series, brain CT, isotope nuclear brain scan, and carotid arteriograms were reportedly normal. Administration of phenytoin, minor tranquilizers, and tricyclic antidepressants did not afford relief.

Nine months after onset, the physical examination was normal except for a high-pitched pulsatile bruit audible just anterior to the right ear. The bruit was loud enough to be heard by the examiner standing next to the patient without the use of a stethoscope. Compression of the right jugular vein abolished the bruit, whereas compression of the left jugular vein increased its intensity. An enlarged sella with thinning of the floor was seen on skull films. CT revealed mild enlargement of the lateral ventricles and an empty sella. Tomograms of the jugular bulb and middle ear were normal. Right retrograde jugular venogram and right retrograde brachial angiogram were normal, including views of intracranial venous sinuses. Opening pressures on multiple lumbar punctures ranged from 260 to 340 mm H_2O. Cerebrospinal fluid chemical, microscopic, microbiological, and serological studies were normal. With the lumbar puncture needle in place, light pressure over the right jugular region caused the bruit to disappear, but there was a consistent 70 to 100 mm H_2O increase in the spinal fluid pressure. Similar compression over the left jugular region increased the intensity of the bruit and produced only slight further elevation of the baseline pressure. During every lumbar puncture, 20 to 30 cc's of CSF were