

Medroxyprogesterone Acetate-Induced Mania in a Patient with Bipolar Affective Disorder

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ABSTRACT

Medroxyprogesterone acetate-induced mania in a patient with bipolar affective disorder

Medroxyprogesterone acetate (MPA) is a steroidal progestin which is used as a contraceptive, in hormone replacement therapy, dysmenorrhea and amenorrhea. A 19-year-old female with bipolar affective disorder who was started on MPA for the treatment of secondary amenorrhea developed manic episodes while taking MPA pills. She was in remission for three years when MPA was commenced. As manic symptoms emerged following the onset of MPA treatment, risperidone and valproic acid was administered, which was then switched to aripiprazole and lithium treatment because of side effects. The manic episode resolved three weeks after hospital admission. This case report highlights the risk of commencing hormone pills in patients with personal history of affective disorders because of the possibility of MPA-induced manic episode.

Keywords: Bipolar affective disorder, manic episode, medroxyprogesterone acetate

ÖZET

İki uçlu duygudurum bozukluğu olan bir hastada medroksiprogesteron asetat ile indüklenen mani

Medroksiprogesteron asetat (MPA), doğum kontrolünde, hormon yerine koyma tedavisinde, dismenorede ve amenorede kullanılan bir steroid progestindir. Sekonder amenore tedavisi için MPA başlanan iki uçlu duygudurum bozukluğu olan 19 yaşında kadın hastada MPA ilacı kullanırken manik kayma gözlemlendi. Hasta MPA tedavisi başlandığında 3 yıldır remisyondaydı. MPA tedavisinin başlanmasından sonra manik belirtilerin ortaya çıkmasıyla hastaya önce risperidon ve valproik asit tedavisi başlandı, ardından yan etkiler nedeniyle aripiprazol ve lityum tedavisine geçildi. Manik epizodla hastaneye yatırıldıktan 3 hafta sonra iyileşti. Bu vaka MPA'nın düşük olasılıkla da olsa manik epizodu indükleyebileceği ihtimalini öne sürerek geçmiş öyküsünde iki uçlu duygudurum bozukluğu olan hastalarda hormon tedavisi başlarken risklerin dikkate alınması gerekliliğini vurgulamaktadır.

Anahtar kelimeler: İki uçlu duygudurum bozukluğu, manik epizod, medroksiprogesteron asetat



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INTRODUCTION

Medroxyprogesterone acetate (MPA) is a steroidal progestin, a synthetic variant of the steroid hormone progesteron (1,2). It has an antiestrogenic effect by inhibiting gonadotropin secretion (3). On the other hand, MPA has androgenic activity and also induces glucocorticoid activity when administered at very high doses (4). It is used as a contraceptive, in hormone replacement therapy, and for the treatment of endometriosis, dysmenorrhea

and amenorrhea (2). With this, depression is one of the most common psychiatric side effects of progesterons (5,6). MPA is thought to cause mood changes and the results of recent studies suggest that it may have a role in the regulation of manic symptoms (7,8). To our knowledge, in the literature, there is only one case report on MPA-induced manic symptoms (9). In this report, we sought to discuss the possible induction of manic symptoms by oral MPA through a case report with bipolar affective disorder.

CASE

A 19-year-old female presented to our clinic with a history of bipolar affective disorder for three years with normal sexual development and standard secondary sexual characteristics whose menarche was at age 13 but menses ceased three years ago, likely after hyperprolactinemia with risperidone treatment. She was diagnosed with secondary amenorrhea. A gynecologist prescribed her MPA (10mg/day) pills for amenorrhea 10 days before hospitalization. She began to suffer from insomnia two days after beginning MPA treatment. She started feeling herself energized in the following days with symptoms such as irritable mood, feelings of anger, increased talkativeness, increase in goal-directed activity and an expression of increased libido. After the 10th day, she stopped MPA treatment, withdrawal bleeding occurred and she was admitted to the hospital with manic episodes. The Young Mania Rating Scale (YMRS) (10) score was 32 at the time of hospital admission with the symptoms described. Physical examination of the patient was normal. Blood samples, including sex hormone tests, full blood count, full blood chemistry profile and thyroid function tests, were reported as normal. The patient was told that any stressful or unusual life events might affect her biorhythms.

As manic symptoms emerged, risperidone and valproic acid was administered based on knowledge of these medications being efficient for symptom control during her previous episodes. Her manic symptoms resolved three weeks after hospital admission. Hyperprolactinemia side effects of risperidone had negative effects on the patient's treatment adherence. Medications were then switched to aripiprazole and lithium. The YMRS score was 7 at the end of three weeks of hospitalization.

It was the second psychiatric hospitalization of this patient. She was initially hospitalized for two months with manic episode three years ago when she had been treated successfully with risperidone at 2mg/day and valproic acid at 1000mg/day. Antipsychotic medication with olanzapine at 20mg/day was not

efficient in symptom control during her recent hospitalization. She was discharged from the hospital after improvement in symptoms with risperidone and valproic acid treatment. In the follow-up examinations, risperidone medication was reduced gradually and ceased because of elevating prolactin hormone levels in the range of 32.4ng/mL and 78.9ng/mL (normal range: 4.79ng/mL-23.30ng/mL), causing amenorrhea and galactorrhea. Brain magnetic resonance imaging was performed and showed no evidence of pituitary microadenoma. She stopped taking valproic acid medication of her own volition 18 months after the first manic episodes because of weight gain. She refused to use any medication other than quetiapine despite psycho-education on bipolar affective disorder. She only took quetiapine at 12.5mg/day for sleeping problems for nearly two years. She had neither manic nor depressive episodes during the previous three years, and was in remission for three years when MPA was prescribed.

In terms of time course, the patient was followed up with once a month as an outpatient with aripiprazole at 5mg/day and lithium at 600mg/day (serum level: 0.5-0.8mmol/l). She had been well-maintained on this treatment. The time between the last manic episode and last examination was 12 months and the patient was euthymic during this period with prolactin levels falling within normal ranges.

We obtained written informed consent from the patient and from her first-degree relative.

DISCUSSION

The case we present in this report has a few points worth discussing. The main issue is the possible unexpected side effects of MPA. The patient was not on any medication other than MPA and quetiapine (12.5mg/day) that would be expected to induce manic episodes. Normal physical examination and blood tests performed upon admission exclude other organic causes. Therefore, the onset of affective symptoms underscores the time correlation between MPA and the manic

episodes. The other matter to consider is the probable side effects of antipsychotics and mood stabilizers for hyperprolactinemia and weight gain. We discontinued risperidone treatment as a consequence of hyperprolactinemia and started on aripiprazole treatment to reduce prolactin levels that were elevated by antipsychotic drugs (11,12).

Medroxyprogesterone, like other progestins, may cause nervousness, sleep problems such as insomnia, somnolence, changes in mood or libido, and emotional lability (5-8). Increases in aggression during MPA treatment have also been reported because of the production of negative affect (6). All these symptoms occurred in patients receiving MPA and were described as main adverse effects of the drug. However, little is known about its effects within the central nervous system. Besides the progestogenic effect, which is in common for all progestins, there is a wide range of biological effects of MPA, including androgenic properties based on low or high doses and the variety of tissues. The overall biological effect of MPA is determined by the sum of all conditions that may explain its adverse effects.

In the case presented here, adverse mood side effects of MPA treatment might be one of the suspicious reasons contributing to bipolar disorder and insomnia. In our patient, insomnia was the first symptom following administration of MPA. It is known that sleep loss contributes to the onset or progression of manic or hypomanic episodes in patients with bipolar disorder (13).

Besides, our patient had not been taking effective prophylactic treatment during the course of their MPA administration because of treatment nonadherence. Although the onset of affective symptoms and the course of illness indicate a time correlation between MPA and manic episode, it is difficult to explain the relationship between manic induction and MPA treatment. On the other hand, a patient with bipolar disorder that presents a manic induction after MPA treatment while taking efficient prophylactic treatment with valproic acid at 2000mg/day (serum level: 69.8µg/mL) and antipsychotics was reported recently (9). Therefore,

manic induction in our case may be the result of both discontinuation of prophylactic treatment and MPA treatment.

The results of a study investigating the mood effects of progestins support that progestins do not induce depression. In this study, it was also reported that MPA may improve negative mood (14). In another study comparing adverse effects of two different doses of MPA during postmenopausal hormone replacement therapy, the authors reported that physical symptoms did not differ between 10 and 20mg MPA, but more negative mood symptoms were observed with the lower dose of MPA while the higher MPA dosage enhanced positive mood symptoms (15). However, it was also described that the addition of progestins during hormone therapy increases negative mood and physical symptoms (16). The lack of consistency on adverse effects of MPA confirms that the differential effects on mood from MPA are still unknown (17).

Recent studies have suggested that hormone treatments, such as selective estrogen receptor modulators or progestins, may be useful in the treatment of mania. Estrogen and progesterone combinations appear to be effective as adjuvant treatment for mood stabilization. MPA may have benefits in the treatment of manic symptoms, just as described recently (7,8). In the case presented here, the lack of mood stabilizing effect from MPA treatment could be as a consequence of dosage. As 10mg/day dosage of MPA is known to be effective in the treatment of secondary amenorrhea, and the attending gynecologist for our case used MPA at dose of 10mg/day for 10 days. However, participants of the aforementioned study received MPA at 20mg daily for 28 days (8). As such, it seems that varied doses of MPA may be necessary to elicit unique treatment outcomes.

Commencing hormone pills for the treatment of menstrual problems of patients with affective disorders can cause the emergence of secondary problems. Hormone treatments, including MPA, are often prescribed with a lack of knowledge of patients' psychiatric history and their effects on psychiatric disorders. As there is only one previous investigation

in the literature on MPA inducing manic episodes in bipolar affective disorder patients, our report may also lead further research on the issue.

Contribution Categories	Name of Author
Follow up of the case	M.A., A.K., I.E.
Literature review	M.A., B.C.I., A.K.
Manuscript writing	M.A., B.C.I., A.K., I.E.
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