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Manic Symptoms Associated with Isotretinoin and Methylphenidate Combination: a Case Report

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ÖZET:

İsotretinoin ve metilfenidat kombinasyonuyla ortaya çıkan manik semptomlar: Bir olgu sunumu

İsotretinoin (Roacutane TM), akne vulgaris ve başka bazı dermatolojik hastalıkların tedavisinde kullanılan, çeşitli ruhsal yan etkiler yaptığı bilinen sentetik retinoid bir ilaçtır. Bu olgu sunumunda 18 yaşında Dikkat Eksikliği Hiperaktivite Bozukluğu nedeniyle metilfenidat (Concerta TM) kullanan bir kadın hastada isotretinoin ve metilfenidat kombinasyonuyla manik semptomların ortaya çıktığı bildirilmektedir. Olguda ya da ailesinde bipolar bozukluk öyküsü mevcut değildi. Metilfenidat ve isotretinoin'in ayrı ayrı manik semptomlara yol açabileceğine dair bildirimler mevcut olmakla birlikte yazımız her iki ilacın manik semptom ortaya çıkarıcı etkilerinin additif olabileceğine işaret eden ilk olgu bildirimidir.

Anahtar sözcükler: isotretinoin, metilfenidat, tedavi, mani

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ABSTRACT:

Manic symptoms associated with isotretinoin and methylphenidate combination: a case report

Isotretinoin (Roaccutane™) is a systemic synthetic retinoid used to treat acne vulgaris and some other dermatological diseases. Isotretinoin is associated with several psychiatric side effects. This case report describes an 18-year-old female patient with Attention Deficit Hyperactivity Disorder, who developed manic symptoms during isotretinoin and methylphenidate (Concerta™) combination treatment. She had no personal or family history of bipolar disorder. Although there are reports suggesting that both isotretinoin and methylphenidate may be separately associated with manic symptoms, to our knowledge, this is the first case report describing that manic symptoms might emerge as a result of the additive effect of combined isotretinoin and methylphenidate treatment.

Keywords: isotretinoin, methylphenidate, treatment, mania

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INTRODUCTION

Isotretinoin (13-cis-retinoic acid) is a systemic synthetic retinoid used in treatment of moderate to severe acne vulgaris that does not respond to other therapies and of lesions associated with some other dermatologic diseases , e.g., psoriasis, hydradenitis suppurativa, ichthyosis, lupus erythematosus, severe acne rosacea, and various skin cancers[1]. Mucosal dryness and itching are the most common side effects of isotretinoin. Possible development of serious mental health problems associated with isotretinoin is among the most important warnings in the related patient instruction manual prepared by the FDA[2]. The manual strongly advises patients to discontinue the drug and consult a physician immediately if they: a) start to feel sad or have crying spells; b) lose interest in activities they once enjoyed; c) sleep too much or have trouble sleeping; d) become more irritable, angry, or aggressive than usual; e) have a change in appetite or body weight; f) have trouble concentrating; g) withdraw from friends or family; h) feel like they have no energy; i) have feelings of worthlessness or guilt; j) start having

thoughts about hurting themselves or taking their own life (suicidal thoughts); k) start acting on dangerous impulses; l) start seeing or hearing things that are not real.

Although the association between isotretinoin and psychiatric symptoms is controversial, it is known that it could cause depression, a tendency to commit suicide, and psychotic findings[3]. There is no known drug interaction of isotretinoin and methylphenidate.

Cases of manic tendency associated with the use of several drugs, mainly with antidepressants, have been reported. There are case reports suggesting that isotretinoin and methylphenidate, the subject matter of this case report, can separately cause manic symptoms. Psychosis and mania are reported as side effects of stimulant drugs[4]. When they retrospectively evaluated the effects of stimulant drugs used for treatment of concomitant ADHD or depression in 137 adult patients followed-up for a diagnosis of bipolar disorder, Wingo and Ghaemi reported the rate of the patients who experienced mania/hypomania associated with stimulants to be 40 percent[5].

Koehler-Troy et al. reported a mania case associated with methylphenidate use in a 10-year-old ADHD patient with a positive family history of bipolar disease. The authors warned that care should be taken when prescribing stimulants, especially in cases with a family history of bipolar disorder[6].

In a study based on the reports of the US Food and Drug Administration (FDA), "Mania" was investigated in 27,007 patients who received isotretinoin (Accutane™)[7]. In thisstudy, 27,007 patients receiving isotretinoin had reported side effects as of February, 2014. It is stated that 55 (0.20%) of these patients reported "Mania" as a side effect. It was reported that when mania emerged, 25% of the patients had been receiving isotretinoin for less than a month; 40.62% for 1 to 6 months; 18.75% for 6 to 12 months; 3.12% for 1 to 2 years; and 12.5% for 2 to 5 years.

As far as we know, manic symptoms associated with the combination of isotretinoin and methylphenidate have not been reported previously. This case report demonstrates that the occurrence of manic symptoms was facilitated, when isotretinoin and methylphenidate were used in combination, and thus, additive effects might arise in terms of the effects (side effects) of these two drugs.

CASE

An eighteen-year-old female patient was admitted to our psychiatry outpatient clinic with a complaint of inability to pay attention while getting prepared for the university entrance examinations. The patient, who stated she had had "attention deficit" symptoms in the forms of "difficulty to pay attention to details, making careless mistakes in school activities", "difficulty to maintain concentration in duties or activities that require attention", "difficulty in completing school assignments regardless of difficulty in understanding instructions", "avoiding tasks that require prolonged mental effort, disliking such tasks and unwillingness to commit such tasks", "distractibility" and "hyperactivity/impulsiveness" symptoms in forms of "fidgety hands and feet, restlessness while sitting" for a long time and stated that during her childhood years prior to age 12, she had problems of "poor concentration", "carelessness, daydreaming", "being quick-tempered, angered", "difficulty in pursuing, following or completing a task she had started". The patient was diagnosed with ADHD-B (combined type). The patient received a total score of 61 when she was evaluated with the Adult ADD/ADHD DSM IV-Based Diagnostic Screening and Rating Scale, for which Günay et al. performed the validity reliability study[8]. Günay et al. reported that those with a score above 59 demonstrate a high degree of ADHD symptoms.

Methylphenidate extended release tablet was started at a dosage of 18 mg/day. Since she could "sit down to study her lessons somewhat easier" with the initial dosage of 18 mg and as she did not experience any side effects, the dosage was increased to 36 mg. Because she complained of nausea with the 36 mg dosage, the treatment was readjusted so

that a divided dosage of 18 mg was taken in the morning and at noon. As there was not any obvious improvement with 36 mg and as the nausea complaint discontinued, the dosage was increased to 54 mg as a single daily dose. Meanwhile, it was learned that isotretinoin 30 mg was started by a dermatologist for acne treatment. The patient, who received isotretinoin for a short time while the methylphenidate dosage was 36 mg, did not report any side effects during that period. Requesting an early appointment the next week, the patient complained of euphoria, acceleration in mental activity, feeling more energetic physically and a need for continuously moving around at home, grandiosity, logorrhea, a reduction in the need for sleep starting 2 hours after taking the pill and she reported that these complaints continued until she hardly falls asleep at night. She stated that she tried not to take methylphenidate for one day and added that she did not experience the side effects on that day. She also articulated that she did not experience the side effects on the days which she took methylphenidate only and did not use isotretinoin. Considering that different forms of methylphenidate might not induce side effects, short acting methylphenidate (Ritalin™) was started. The patient stated that she experienced the same side effects with short acting methylphenidate at the 10 mg/day dosage. Since manic symptoms resolved rapidly when stimulant treatment was discontinued, no additional treatment was arranged. Because the patient stated that she wanted to complete the acne treatment, it was decided to postpone the stimulant treatment.

DISCUSSION

Due to the psychological burden it creates, acne on its own can lead to depressive symptoms irrespective of any side effects of medication(s) used for its treatment[9]. However, the mania-inducing effect does not seem to be easily attributable to the psychological burden of acne.

In a study conducted on 55,825 patients who were admitted with acne and other dermatologic problems, Gupta et al. reported that Attention Deficit Hyperactivity Disorder was 2 times higher in acne cases when age, sex, and other factors were controlled[10]. A higher frequency of ADHD in acne cases renders prospective side effects associated with the methylphenidate-isotretinoin combination more important.

Although the mechanism of action of isotretinoin is not exactly known, a small number of studies have reported that isotretinoin induces apoptosis (cell death) in such various cells as the meibomian glands[11,12], hypothalamus cells[13], hippocampus cells[14,15], and sebaceous glands[16,17]. In another study, it was found that isotretinoin significantly altered the expression of hundreds of genes in the skin after eight weeks of treatment[18]. In light of current knowledge, stating whether the effects on apoptosis and gene expression play a role in its combination with methylphenidate does not seem to be possible.

In an article where they discussed the association between depression and retinoic acid, Bremmer et al. suggest that because depression emerges 1-2 months after initiation of treatment, it is more likely for isotretinoin to act through a secondary system or possibly neuroplasticity or a metabolic process rather than through acute actions on a neurotransmitter or another signal pathway[19]. The emergence of manic symptoms after at least one month of isotretinoin use in the vast majority of the cases reported to develop manic symptoms upon the use of isotretinoin[7] suggests that isotretinoin could lead to manic symptoms through a similar process. In our case, however, manic symptoms occurred on the same day, in which the isotretinoin and methylphenidate combination took place. This difference suggests that a distinct mechanism could be playing a role in the appearance of manic symptoms with the isotretinoin and methylphenidate combination.

This case shows that caution should be taken in terms of manic symptoms in patients who receive a combination of isotretinoin and methylphenidate. It seems likely that both drugs could be acting additively in the occurrence of manic symptoms as a side effect. It is not yet possible for us to provide a clear explanation for the mechanism of the side effect.

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