Valproate Induced Agitation and Irritability in a Patient With Mania: Case Report

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ÖZET:
Bir manik hastada valproata bağlı ajitasyon ve irritabilite: olgu sunumu

Valproat duygudurum düzenleyici özellikleri olan bir antikonvülzan ilaçtır. Aynı zamanda ajitasyon, irritabilite ve dürtüsel saldırgan davranışlar ile başa çıkmak için de kullanılır. Bu yazıda 35 yaşında, bipolar bozukluğu olan ve valproat tedavisi sırasında beklenenin tersine ajitasyon ve irritabilite gelişen bir olgunun sunumu amaçlanmıştır. Hastanın 10 yıldır bipolar bozukluk tanısı vardı ve hastanemize manik dönemde yatırılmıştı. Yatışında öforik olsa da irritabilitesi yoktu. Valproat ve diazepam tedavisi başlandı. Yatışının dördüncü gününde irritabilite, ajitasyon ve hostilite ortaya çıktı. Geçmiş sağlık kayıtları incelendiğinde önceden de valproat tedavisi sırasında ajitasyon ve şiddet gösterdiği saptandı. Valproatın kesilmesiyle ajitasyon ve irritabilite hızla düzeldi. Olgu lityum ile iki haftalık tedavi sonrasında hastaneden remisyon ile taburcu edildi. Eğer bir hastada valproat başlanmasından sonra irritabilite ya da ajitasyon ortaya çıkarsa ya da ajitasyon ve irritabiliteyi düzeltmek amacıyla valproat başlandıktan sonra durum daha da kötüleşirse bunun valproatın yan etkisi olabileceği akılda tutulmalıdır.

Anahtar sözcükler: Valproat, ajitasyon, irritabilite, advers olaylar

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ABSTRACT:
Valproate induced agitation and irritability in a patient with mania: case report

Valproate is a mood-stabilizing anticonvulsant. It is also used in the management of agitation, irritability and impulsive aggressive behavior. Here we report on a 35-year-old male with bipolar disorder who had paradoxical agitation and irritability during valproate therapy. He had bipolar disorder for ten years and he was hospitalized due to his manic episode. At the time of admission he was euphoric but not irritable. He was put on valproate and diazepam. On the fourth day of valproate therapy he became irritable, agitated and hostile. Careful investigation of his previous health records showed that he had had a history of agitation and violence in the past while he was on valproate therapy. His agitation and irritability improved rapidly after discontinuation of valproate. He was discharged from the hospital in remission after two weeks of therapy with lithium. If a patient develops new-onset agitation and irritability or worsening of agitation and irritability after starting valproate for the treatment of agitation and aggression, one needs to consider that this may be a manifestation of an adverse effect of valproate.

Key words: Valproate, agitation, irritability, adverse reactions

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INTRODUCTION

Valproate is a mood-stabilizing anticonvulsant approved by the U.S. Food and Drug Administration (FDA) for the treatment of manic episodes associated with bipolar disorder, epilepsy, and prophylaxis of migraine. Its efficacy in manic episodes is comparable to that of lithium and carbamazepine (1). It is a simple branched-chain carboxylic acid with a half-life of 10 to 16 hours. The therapeutic serum concentration of valproate is believed to be between 50 and 150 μg/ml. It is generally well tolerated, but it has several side effects such as tremor, gastrointestinal distress, sedation, benign hepatic transaminase elevation, leukopenia, thrombocytopenia, hair loss, and weight gain. Rare serious adverse reactions include hepatic failure, pancreatitis, and hyperammonemia (2,3). A case of valproate induced delirium has been reported recently (4). Here we report a very rare case of valproate induced agitation and irritability.

CASE REPORT

Mr. G is a 35-year-old male who was living alone. He had bipolar disorder for 10 years. He had experienced three depressive episodes and one manic episode. He had been hospitalized once before due to a depressive episode. He was poorly compliant with medications and seldom took them on a regular basis. He was admitted to the psychiatry clinic of Ataturk Education and Research Hospital. He had elation, grandiosity, pressured speech, distractibility, and decreased need for sleep. His colleagues stated that during the previous week, he had been very

energetic and he had mentioned many new projects, some of which seemed extraordinary to them. He did not fulfill the DSM-IV criteria for any other axis I or axis II disorder. He was medically healthy. He had not had any serious medical problems, except for meningitis when he was five years old that ended with full recovery and without any sequelae. His complete blood count, liver and kidney function tests, thyroid profile and urine analysis were within normal limits. His urine drug screen was negative.

Upon admission, his Young Mania Rating Scale (YMRS) (5,6) score was 34. He was put on valproate sodium 500 mg twice daily and diazepam 5 mg twice daily. On the fourth day of valproate therapy, his distractibility increased. He became irritable and agitated. He began to swear loudly. During lunch, he knocked over his food tray and tried to break the windows. He was hostile to other patients and tried to hit them. He had to be restrained on several occasions for safety. Diazepam dosage was gradually increased to 30 mg per day to which he responded with mild sedation. His YMRS score was 51 and his serum valproate level was 103.2 μg/ml on the fifth day of valproate therapy.

When his ex-wife was contacted, it was learnt that he had been prescribed valproate 3 years earlier during his first hospitalization. His ex-wife mentioned that he had become agitated and even violent while he was on valproate. When valproate was stopped, he improved dramatically in a few days. As soon as we confirmed this information with the patient's medical records, we discontinued valproate. The following day, Mr. G became more cooperative and less irritable. He apologized for his inappropriate behavior. Three days later, he was no longer irritable, but was as cheerful and energetic as on the day of his admission. Lithium 900 mg per day was started and the dosage was increased to 1200 mg per day until blood lithium concentration was 0.83 mEq/l. After he achieved remission, the diazepam was tapered off gradually and discontinued. He had not received any antipsychotics or any other drugs during his hospitalization. He was discharged from the hospital in remission within two weeks. His YMRS score was 5 on the day of his discharge.

DISCUSSION

There is scant information about the behavioral side effects of valproate, most of the data coming from pediatric patients with epilepsy. Firstly, aggressiveness was reported in three epileptic children on valproate monotherapy (7). Subsequently, bizarre behavior and hallucinations were reported in a 14-year-old boy who used sodium valproate for convulsions (8). Coulter et al. used valproic acid in children with uncontrolled seizures and reported that valproic acid therapy adversely affected 8 children out of 100, causing belligerent behavior or hallucinations (9). A study that examined 88 pediatric patients with seizure disorders who were on valproate monotherapy reported behavioral alterations in 42% of patients, including irritability, hyperactivity, and aggressiveness (10). Another study noted that 25% of children with complex partial seizures treated with valproate developed hyperactivity, irritability, and aggression, that were severe enough to discontinue or decrease valproate (11).

There is less information on behavioral side effects of valproate in adults. Alvarez et al. reported a 35-year-old male with a seizure disorder who became disoriented, belligerent, and agitated while he was receiving valproate along with phenytoin, phenobarbital, and thioridazine (12). Sobhan et al. reported a 39-year-old male with schizoaffective disorder who experienced agitation as a side effect of divalproex sodium (13). Sobhan's case was also receiving fluphenazine, benztropine, and clonazepam concurrently. Mr. G did not receive any other drugs with valproate except diazepam. He had a history of agitation with valproate in the past which resolved after discontinuation of valproate therapy. Therefore compared to the other two cases mentioned above, we can establish a more definite relationship between his agitation and valproate ingestion. In addition, his Naranjo Adverse Drug Reactions Probability Scale (14) score was 9, which points out a definite relationship.

Therapy with anticonvulsant drugs may have behavioral consequences (15). Although valproate seems to be effective in agitation, irritability, and impulsive aggressive behavior (16-19), if a patient develops new-onset agitation and irritability or worsening of agitation and irritability after starting valproate for the treatment of agitation and aggression, one needs to consider that this may be a manifestation of an adverse effect of valproate. To the best of our knowledge, this is the first reported adult patient with bipolar disorder who has exhibited paradoxical agitation with valproate.

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