

Sodium valproate-induced isolated thrombocytopenia

Sodyum valproat kullanımına bağlı izole trombositopeni

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ABSTRACT

Sodium valproate is one of the medications used in the treatment of the schizoaffective disorder, bipolar disorder, and epilepsy. Tremor, drowsiness, Reye-like syndrome, hepatic failure, thrombocytopenia, pancreatitis are the most frequent side effects of this medication. Thrombocytopenia is another serious side effect of sodium valproate. Here, we report the case of a patient with thrombocytopenia associated with sodium valproate.

Keywords: Sodium valproate, thrombocytopenia, side effect, bipolar disorder

ÖZ

Sodyum valproate şizoaftektif bozukluk, bipolar bozukluk ve epilepsi tedavisinde kullanılan ilaçlardan biridir. Tremor, halsizlik, Reye benzeri sendrom, karaciğer yetmezliği, pankreatit bu ilacın yan etkilerinden bazılarıdır. Trombositopeni, sodyum valproatın bir başka ciddi yan etkisidir. Burada, sodyum valproat ile ilişkili izole trombositopenili bir olguyu literatür bilgileri ışığında ele aldık.

Anahtar Kelimeler: Sodyum valproat, trombositopeni, yan etki, bipolar bozukluk

INTRODUCTION

Sodium valproate is a commonly used medication in the management of the schizoaffective disorder, bipolar disorder, and epilepsy with good response (1). Sodium valproate has psychiatric, neurological, dermatological, immunological, metabolic, gastroenterological and hematological side effects (2). Thrombocytopenia is one of the hematological side effects of sodium valproate. Although not life threatening, it is a side effect that reduces the quality of life (1). Although there are cases reported in the literature, there is limited information about the effects of repetitive use on treatment compliance of

the patient. Herein, we presented the treatment process and the training process related to compliance with the treatment of a female patient who had side effects of isolated thrombocytopenia due to sodium valproate four times in different hospitals and times.

CASE PRESENTATION

A 31 years old, single, unemployed, female patient was being followed up at different psychiatry outpatient clinics for 10 years with a diagnosis of bipolar disorder type 1. She was using clozapine 400 mg/day per oral (PO) for three months in another clinic.

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Her manic symptoms were not taken under control with this treatment, and the parents stated the increased sexual desire, having a decreased need for sleep, feeling overly happy, feeling restless. She was hospitalized with the diagnosis of bipolar disorder according to Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (3). Previously prescribed drugs used by the patient at the effective dose and time were aripiprazole, quetiapine, haloperidol, chlorpromazine, lithium, olanzapine, carbamazepine, risperidone, and a few combinations such as aripiprazole-quetiapine, quetiapine-olanzapine, olanzapine-chlorpromazine, carbamazepine-quetiapine-chlorpromazine, etc. According to the story taken from her mother, the patient discontinued lithium because she could not tolerate side effects such as nausea and vomiting, and she did not get enough benefit from carbamazepine. She did not remember whether or not he used sodium valproate. Sodium valproate 250 mg/day PO was added to clozapine 400 mg/day PO and it was titrated up to 1000 mg/day PO as a mood stabilizer. The patients and their relatives were informed about the effects and possible side effects of the treatment. The patient's initial baseline laboratory data at the time of admission for some hematologic parameters were white blood cell (WBC) 7.9 ($10^3/\mu\text{L}$), haemoglobin (HGB) 11.63 (g/dL), haematocrit 36.75 (%), mean corpuscular volume (MCV) 83.23 (fL), platelet (PLT) 178.9 ($10^3/\mu\text{L}$), plateletcrit 0.1240 (%), mean platelet volume 6.93 (fL), ferritin 24.6 ng/mL. In hematological analyses two weeks after titrating sodium valproate to 1000 mg/day PO, the serum sodium valproate level was found to be 86.9 mg/L (day 1 of thrombocytopenia according to the laboratory data). WBC, HGB, MCV levels were at normal ranges but PLT was 81.9 ($10^3/\mu\text{L}$). The patient's thyroid, renal, and liver function tests were within normal limits. A history of smoking, alcohol and substance abuse was not available. Her family history was unremarkable apart from sustained vitamin B12 deficiency in her mother. The newly developed thrombocytopenia was attributed to sodium valproate and it was discontinued. Peripheral blood film revealed normocytic normochromic red blood cells, WBCs were adequate with normal morphology and it indicated thrombocytopenia. Clinical hematology consult was taken and they made a provisional diagnosis of sodium valproate-induced thrombocytopenia. PLT count increased to 92.1 ($10^3/\mu\text{L}$), 95.5 ($10^3/\mu\text{L}$), 150.0 ($10^3/\mu\text{L}$), 178.8 ($10^3/\mu\text{L}$) on days 3, 6, 8, and 12, respectively. His father came to visit for the first time on the 20th day of his hospitalization, said the patient had a history of sodium valproate use and associated nose and gingival bleeding in different three times. Sodium valproate-induced thrombocytopenia was observed in different clinics and the family were warned about this side effect. The patient had

thrombocytopenia due to sodium valproate use for the fourth time due to inadequate family support and mother's forgetfulness due to vitamin B12 deficiency. No additional treatment was applied for the reduction of thrombocytopenia. Carbamazepine 200 mg/day PO was added to clozapine 400 mg/day PO and it was titrated up to 800 mg/day PO. No similar side effects were reported during the follow-up of the patient. Psychiatric complaints decreased significantly. The patient and his relatives were warned of edema due to sodium valproate use and informed consent was obtained from them for their knowledges. Naranjo Adverse Drug Reaction Probability Scale (NADRPS) score of the patient was 10 (4).

DISCUSSION

This case report was evaluated as a case of thrombocytopenia due to sodium valproate. Because there was a temporal relationship between them, the side effect began with the addition of the drug and completely cured after discontinuation of the drug. In addition, other examinations were normal. On the other hand, the patient has a history of sodium valproate-induced thrombocytopenia. The NADRPS score indicates a definite association between drug use and side effect (4). The mechanism by which sodium valproate could cause thrombocytopenia has not been fully elucidated. Possible explanations include peripheral platelet destruction and suppression of the bone marrow production. According to the study of Kurahashi et al. (5), thrombocytopenia in patients treated with sodium valproate will not be attributable to bone marrow suppression of platelet production. Peripheral platelet destruction is more likely the cause of the thrombocytopenia in patients treated with sodium valproate. The risk factors of sodium valproate-associated thrombocytopenia appear to be advanced age, female gender, and high doses (6). In a double-blind trial,

Nasreddine and Beydoun (7) demonstrated an association between sodium valproate therapy and thrombocytopenia and a negative correlation between plasma sodium valproate level and platelet count. Despite the fact that our patient was young and did not use any toxic dose of medication, side effects occurred. Thrombocytopenia often goes unnoticed and can suddenly manifest with life-threatening events such as hemorrhagic stroke or bleeding (6). Some antipsychotics such as clozapine can cause hematological side effects. Bipolar disorder, independently from treatment with atypical antipsychotics, have a higher frequency of diabetes and metabolic syndrome than the general population, so treatment with sodium valproate may expose bipolar patients to a further risk of cardiovascular events as a result of thrombocytopenia (6).

In terms of drug interactions, Facciola et al. (8) stated that sodium valproate may have an inhibiting effect on the cytochrome P450 (CYP) 1A2- or CYP3A4-mediated conversion of clozapine to norclozapine, so patients comedicated with sodium valproate tended to have higher clozapine levels and lower norclozapine levels, which norclozapine is one of the major metabolites of clozapine. Patients with bipolar disorder are frequently treated with multiple therapies which may increase the risk of bleeding (e.g., mood stabilizers, selective serotonin reuptake inhibitors). When thrombocytopenia occurs, the patient's general medical condition should be reassessed and other organic conditions that may cause thrombocytopenia should be excluded. Dose can be reduced or the drug can be changed (9).

In our patient, there was no need for them, and when the drug was stopped, the thrombocytopenia disappeared. World Health Organisation (WHO) defines 'definite' as an event or laboratory test abnormality, with plausible time relationship to drug intake (10). WHO also says this relationship cannot be explained by disease or other drugs, response to withdrawal plausible (pharmacologically, pathologically), event definitive pharmacologically or phenomenologically (an objective and specific medical disorder or a recognized pharmacological phenomenon), rechallenge (if necessary) (10).

Factors influencing patients with psychiatric disorders compliance with medication include patient-related influences, physician-related variables, factors related to the patient's environment, treatment-related factors, and side effects. The influence of side effects has been demonstrated in patients' noncompliance with treatment. Sometimes, despite the side effects, some patients continue to be exposed to the drug. The level of functioning of the relatives of the patients, psychiatric or medical diseases which they have should be taken into consideration (11,12). In our patient, the patient who had not been properly monitored for side effects due to medication was exposed to thrombocytopenia four times.

CONCLUSION

As a result, this case report suggests that physicians and relatives should be aware that sodium valproate may induce thrombocytopenia with a low quality of life and low compliance. Further systemic research should be conducted with respect to sodium valproate-associated thrombocytopenia to provide a greater understanding of both its prevalence and etiology.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

FINANCIAL DISCLOSURE

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ETHICS

The patient's data was used to write this case report within the context of the institutional local ethics approval.

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