

Valproic Acid-Induced Neutropenia

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- ✓ Valproic acid is an important anticonvulsant agent but it has some serious side effects. Neutropenia is one of them. A one-year old female patient applied to our hospital for control. Neutropenia was determined in her complete blood count. She was given some specific diagnostic tests to explain the cause of neutropenia. At the end of the evaluation, it was thought that neutropenia was due to valproate. The patient's hematological parameters improved after stopping drug apply. This case was found interesting enough to be presented since VPA-induced neutropenia had caused fever.

Key words: Neutropenia, neutropenic fever, valproic acid

✓ **Valproik Aside Bağlı Nötropeni**

Valproik asit, önemli antikonvülzan ajanlardan biri olmakla beraber ciddi yan etkilere sahiptir. Nötropeni bunlardan biridir. Bir yaşında kız hastanın, kontrol muayenesi için başvurduğu sırada yapılan tam kan sayımında, nötropeni saptandı. Yapılan bazı spesifik tanı testlerinden sonra hastanın nötropenisinin valproik aside bağlı olduğu saptandı. Valproik asit tedavisi sonlandırılan hastanın kan değerleri hızla düzeldi. Valproik aside bağlı nötropeni, bu olguda nötropenik ateşe neden olduğu için yayınlamak istedik.

Anahtar kelimeler: Nötropeni, nötropenik ateş, valproik asit

INTRODUCTION

Valproic acid (VPA) is an important anticonvulsant agent, which is commonly used in the treatment of epilepsy. The drug is being used increasingly in higher doses as a single anticonvulsant agent that produces a good response and has an acceptable level of toxicity⁽¹⁾. Hepatotoxicity is the most common widely recognized toxicity. With the use of higher drug levels to achieve adequate seizure control, hematologic toxicity is being increasingly encountered, and the pediatric hematologist is consulted for these problems in the pre-or perioperative setting⁽²⁾. It is supposed that thrombocytopenia results from idiosyncratic and immunologic mechanisms. The mechanism of neutropenia and erythrocyte aplasia is not clear yet⁽³⁾. We are presenting a case with serious neutropenia

and neutropenic fever which depends on valproic acid.

CASE REPORT

A one-year-old girl with epilepsy was admitted to our clinic for control examination. The patient's generalized type seizures were observed when she was hospitalized due to meningitis. Meningitis was treated but the convulsions frequently repeated. Valproic acid was started 15 mg/kg/day in two dose. In order to control her seizures the dose was increased up to 30 mg/kg/day and she was invited to hospital for control 25 days later. At the control examination she had hypoactivity and skin pallor. In complete blood counting; Hb; 8,4gr/dl (mean 12 gr/dl), Hct; 27% (mean 36%), MCV; 62,5 fl (mean 70 fl), MCHC; 20 pg (mean 33 pg), MCH; 30%

(mean 27%), RDW; 21% (mean 20%), the number of erythrocyte; 4,2 million cell/mm³ (mean 4,5 million cell/mm³), the number of thrombocyte; 348000/mm³ (300000-500000/mm³), the number of leukocyte; 934 cell/mm³ (4000-11000 cell/mm³) were obtained. Neutropenia was determined. In the peripheric blood smear; 46% neutrophils, 44% lymphocytes, 8% monocytes, 2% eosinophils were obtained. The absolute neutrophil count; 429 cell/mm³ (normal: 1800-8000), erythrocyte morphology were hypochromic and microcytic. Thrombocytes were in normal range. Bone marrow examination revealed arrest of the maturation of young myeloid series and normal megacaryocyte and increased erythroid cell numbers. It was obvious that there was nothing about the bone marrow infiltration. Viral examinations were negative. Serum-iron level was; 25 mcg/dl (35-155 mcg/dl), the capacity of iron-binding was; 450 mcg/dl (358±38). The level of serum valproate was; 120 mcg/dl (50-100 mcg/dl). According to all these results, it was claimed that the patient's neutropenia was due to VPA treatment and therefore the application of this drug was stopped.

Then, she had a body temperature raising to 39 °C. Neutropenic fever was diagnosed and antibiotic treatment was started. One week later, after VPA treatment was stopped, the patient bone marrow was found normal. (Her white blood cell count had increased.) Clonazepam was started. The patient came back to the hospital for control one month later and her hematologic values were found normal and her seizures were under control.

DISCUSSION

Valproic acid has some serious toxic effects. The most important one of them is

hematological side effect⁽⁴⁾. The most common one is subclinic thrombocytopenia. This effect is thought to be dependent on thrombocyte destruction which was stimulated by antibodies and it can be seen in 40% of the patients⁽⁵⁾. Neutropenia may also be definable and temporary but its mechanism has not been known yet. In 1979, Jaeken J. et al⁽⁶⁾, reported a case with neutropenia depending upon VPA treatment for the first time. They had given VPA treatment (40 mg/kg/day) to a three-month-old infant who had seizures after its anoxic birth and then neutropenia was observed. Her neutrophil count had rapidly fallen under the value of the time before the treatment. Fourteen days later then the VPA treatment stopped, the total neutrophil count started to increase and it reached the values of the time before the treatment in a few weeks. Symon et al⁽⁷⁾, have observed neutropenia depending on VPA in a 9-year-old patient. The number of neutrophil had fallen to 660cell/mm³ after 25 days from the beginning of the treatment. They also reported that this transient phenomenon lasted for 3 days. Bar et al.⁽⁵⁾ have found absolute neutropenia in the 12 of the 45 patients who were taking single VPA treatment. Coulter et al.⁽⁸⁾ have founded neutropenia (2000 cell/mm³) in 27 of the 100 patients who were being treated by VPA . We also met absolute neutropenia in a one-year-old girl patient in whom we started valproic acid for generalized seizures. The patient's neutrophil count, which had rapidly fallen after 3 weeks from the beginning of VPA treatment, started to increase 7 days after VPA was stopped. There wasn't any viral illness in our case. With the bone marrow examination, acute leukemia, aplatic anemia and other malignancies were ruled out. Any microorganisms could not be isolated from

repeated cultures during the fever episodes. This clinical situation, which we determined as neutropenic fever, shows that some other more serious complications can join to the matter even neutropenia is transient. In this report neutropenia and neutropenic fever depending on VPA are emphasized. Consequently, VPA is an agent which is commonly used in convulsive disorders. It must be taken into consideration that thrombocytopenia that is seen in VPA treatment may give some serious temporary complications such as neutropenia and hematological parameters must be closely observed.

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