**Valproic Acid-induced Agranulocytosis**

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**SUMMARY**

Valproic acid is considered to be the most well-tolerated antiepileptic drug. However, few cases of neutropenia or leukopenia caused by valproic acid have been reported. We present a patient who took valproic acid to treat a complication of brain surgery and in whom severe agranulocytosis occurred after 2.5 months. Valproic acid was stopped immediately, and granulocyte colony-stimulating factor was administered for 2 days. The patient’s white blood cell count returned to normal within 2 weeks. The result of bone marrow aspiration was compatible with drug-induced agranulocytosis. This case illustrates that patients who take valproic acid may need regular checking of complete blood cell count. [International Journal of Gerontology 2009; 3(2): 137–139]

Key Words: agranulocytosis, leukopenia, neutropenia, valproic acid

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**Introduction**

Valproic acid is used widely in children and adults for seizure control, and is considered the most well-tolerated antiepileptic drug. The most common hematologic adverse reaction of valproic acid is thrombocytopenia, which is considered to be associated with antibody-mediated platelet destruction. In recent years, a few cases of valproic acid-induced neutropenia or leukopenia have been reported, some caused by a concomitant use of valproic acid and another drug¹, while others were caused by valproic acid only. We report a case of an intracerebral hemorrhage patient, who used valproic acid to treat a complication of surgery, and then suffered from severe agranulocytosis.

**Case Report**

A 75-year-old man was admitted unconscious to the emergency department. His relatives said he had drunk a lot of alcohol the night before and had vomited once. Brain computed tomography was arranged, and the result showed right-sided intracerebral hemorrhage with mid-line shift. The patient was intubated urgently and sent to the operation room for surgery. After surgery, he was admitted to the intensive care unit for further treatment. Unfortunately, he had a seizure the next day and started using valproic acid 600 mg twice a day to treat this complication. He also suffered from an episode of severe sepsis. Antibiotic treatment brought his infection under control. He underwent tracheostomy 4 weeks after admission because of respiratory failure and was then transferred to the respiratory care center. When the patient’s condition was stable, he was discharged 9 weeks 4 days after admission. The last time blood was examined during hospitalization was 1 week prior to the discharge, and the results proved normal (hemoglobin [Hb] 12.8 g/dL, white blood cell count [WBC] 6,100/μL, neutrophils 62.1%). He continued to use valproic acid.

The patient went to the emergency department again 10 days after discharge. He complained of diarrhea and fever lasting more than 6 days. His blood examination showed severe agranulocytosis (Hb 11.3 g/dL, WBC 1,700/μL, neutrophils 1%) with normal liver function. Because of the impression of agranulocytosis and neutropenic fever, he was admitted to...
the ward and started taking empirical broad-spectrum antibiotics. Valproic acid-induced agranulocytosis was highly suspected, so the doctor stopped valproic acid the next day and, instead, began prescribing granulocyte colony-stimulating factor 150 μg daily that same day. His WBC fell to the lowest level later that day with mild anemia and a normal platelet count (WBC 1,000/μL, neutrophils 0%, Hb 9.6 g/dL, platelet count 200,000/μL). Bone marrow biopsy and aspiration were done 4 days later, and the results showed maturation arrest of the myeloid series, with few segmented or band WBC, and an increased eosinophil series, which is clinically compatible with drug-induced agranulocytosis. After the valproic acid treatment was stopped and granulocyte colony-stimulating factor was administered, the patient’s WBC and neutrophils increased to the normal range within 2 weeks. The Table shows the patient’s laboratory data.

The patient’s blood and pus culture revealed *Acinetobacter baumannii* and methicillin-resistant coagulase-negative staphylococci infection. While under antibiotic treatment, his condition improved gradually. During his period of admission, the patient did not have a seizure. When his WBC returned to normal and his infection was also controlled, he was discharged 7 weeks 2 days after the second admission. At the time of writing, he did not use any other antiepileptic drug and his condition and blood count data remained normal.

### Discussion

Immune-mediated destruction of neutrophils and direct toxic effects on bone marrow are considered as the two mechanisms of drug-induced agranulocytosis or neutropenia. Immune forms usually happen days to weeks after starting the drug, while toxic forms may be delayed for months. The mechanism of valproic acid-induced leukopenia is still unclear, and immunofluorescence studies failed to find antibodies against granulocytes.

Valproic acid-induced neutropenia or agranulocytosis is rare, and the phenomenon seems to be transient. O’Connor and colleagues have evaluated the mechanisms of antiepileptic drug-related chronic leukopenia, and suggested a continuation of therapy when the patient’s bone marrow is normal, leukopenia is stable and absolute neutrophil count is normal. Another case reported that a patient’s neutrophil count fell, and recovered without stopping or changing the dosage of valproic acid, but 2 months later, severe neutropenia was noted. Valproic acid was stopped, and the neutrophil count then returned to normal. Our patient was discovered to have severe agranulocytosis 2.5 months after taking valproic acid. According to previous studies, the mechanism of valproic acid-induced agranulocytosis may have a direct toxic effect on bone marrow. However, some cases occurred within a few days, while some occurred after 1 month. These cases demonstrate that the phenomenon of valproic acid-induced neutropenia

### Table

<table>
<thead>
<tr>
<th>Patient blood analysis</th>
<th>First admission</th>
<th>Second admission</th>
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<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 1</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/dL)</strong></td>
<td>12.8</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>Hematocrit (%)</strong></td>
<td>35.7</td>
<td>31.9</td>
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<tr>
<td><strong>Red blood cells (× 10⁶/μL)</strong></td>
<td>6.1</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>White blood cells (× 10³/μL)</strong></td>
<td>62.1</td>
<td>1</td>
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<tr>
<td><strong>Neutrophils (%)</strong></td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Eosinophils (%)</strong></td>
<td>0.4</td>
<td>0</td>
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<tr>
<td><strong>Basophils (%)</strong></td>
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<td><strong>Monocytes (%)</strong></td>
<td>29.4</td>
<td>93</td>
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<tr>
<td><strong>Lymphocytes (%)</strong></td>
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<td>200</td>
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<tr>
<td><strong>Platelets (× 10³/μL)</strong></td>
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</tbody>
</table>
may vary among patients. Because the time between the ingestion of drugs and the onset of agranulocytosis seems to be unpredictable and the symptoms usually go unnoticed, regular blood examinations should be considered.

Watts et al.\(^9\) presented a case of valproic acid-induced severe anemia and mild neutropenia, and evaluated the correlation between the dosage and bone marrow suppression. The result indicated that the inhibition of bone marrow by valproic acid is dose-dependent. The valproic acid level may be normal or lower than the therapeutic range when neutropenia occurs\(^8\). Our patient's valproic acid level was not sampled the next day after the second admission, so we do not know whether the patient’s valproic acid level was high or within the therapeutic range.

A cohort study investigated the frequency of a severe decrease in blood cell count in patients taking antiepileptic drugs\(^10\). The analyses showed that patients older than 60 years had a higher rate of developing a reduction in blood cells, and the rate was not different among various antiepileptic drugs. Another retrospective study reviewed charts of 35 elderly inpatients who received valproic acid treatment, and showed that valproic acid was well tolerated except for one patient who experienced transient leukopenia\(^4\). The safety of valproic acid in elderly patients needs to be confirmed in more studies, and close monitoring may be necessary in the elderly population.

Our patient was not taking any medication other than valproic acid and lansoprazole when agranulocytosis occurred. He continued to use lansoprazole without any adverse reaction, so we excluded it as a possible cause. Use of the Naranjo adverse drug reaction probability scale indicated that valproic acid was the probable cause (score of 7)\(^11\).

The adverse effect of valproic acid which is of most concern to doctors is hepatotoxicity. The case we report here had normal liver function but developed severe agranulocytosis, which resulted in sepsis. Compared with other antiepileptic drugs, valproic acid has fewer adverse effects, but this experience shows us that patients who take valproic acid may need regular complete blood count checks in addition to their liver function tests, most importantly in the first 3 months of their treatment.

References