Valproate-Associated Dysmyelopoiesis in Elderly Patients

Chi-chiu So, MRCPath, and Kit-fai Wong, MD

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Abstract
Sodium valproate is widely prescribed for patients with epilepsy and psychiatric disorders. Hematologic toxic effects have been largely described in pediatric patients, and dysmyelopoiesis is reported rarely. We describe 2 elderly patients with valproate-associated dysmyelopoiesis and postulate that this particular side effect may be much more common than currently recognized. A correct diagnosis is important for acute patient management and for prognostication.

Sodium valproate is effective in controlling all forms of epilepsy. It is a drug of choice in primary generalized epilepsy and in generalized absence and myoclonic seizures. The drug has been used widely in the pediatric age group. Side effects are related mainly to liver toxicity. Hematologic manifestations are less frequently reported, with most cases being described in children or adolescents.1 We describe 2 elderly patients with dysmyelopoiesis associated with valproate therapy.

Case Reports

Case 1
A 62-year-old woman had a long history of primary generalized epilepsy. Valproate monotherapy was started in 1989. Results of a baseline CBC count were normal. Isolated mild thrombocytopenia of 120 to 130 × 10³/µL (120-130 × 10⁹/L; reference range, 145-370 × 10³/µL [145-370 × 10⁹/L]) soon developed and persisted as shown by serial blood monitoring. The serum valproate levels remained in the therapeutic range.

In January 1997, her epileptic control worsened, and the dose of valproate had to be increased from 1,500 mg once daily to 1,500 mg twice daily. Severe pancytopenia developed after 1 month with a hemoglobin level of 8.1 g/dL (81 g/L; reference range 13.4-17.1 g/dL [134-171 g/L]); a mean corpuscular volume of 98 µm³ (98 fL; reference range, 82-97 µm³ [82-97 fL]); a WBC count of 1,800/µL (1.8 × 10⁹/L; reference range, 3,700-9,200/µL [3.7-9.2 × 10⁹/L]) with 61% neutrophils (0.61), 27% lymphocytes (0.27), and 12% monocytes (0.12); and a platelet count of 10 × 10³/µL (10 × 10⁹/L).
Neutrophils with pseudo–Pelger-Huët anomaly were found on peripheral blood smear examination [Image 1A]. Examination of bone marrow aspirates showed normal cellularity with active megaloblastoid erythropoiesis, relatively reduced and left-shift granulopoiesis, and adequate megakaryopoiesis. Many megakaryocytes with multiple separate nuclei were found [Image 1B]. Some erythroblasts had irregular to lobulated nuclei [Image 1C]. Blasts were not increased, and there were no ringed sideroblasts. A diagnosis of dysmyelopoiesis was made and the possibility of valproate-related hematologic toxic effects was suggested.

The serum valproate level was markedly elevated to 1,447 µmol/L (therapeutic level, 347-693 µmol/L). Valproate therapy was stopped, and carbamazepine therapy was started. Her blood counts normalized 6 weeks after cessation of therapy. In 1999, valproate had to be reintroduced at a reduced dose of 300 mg twice daily in addition to carbamazepine because of poor seizure control. Mild thrombocytopenia recurred, and serial blood monitoring revealed that it remained stable at around 100 × 10^3/µL (100 × 10^9/L).

Case 2

A 62-year-old man had a cerebrovascular accident that was complicated by seizure attacks. He was given 200 mg of valproate twice daily for seizure control. Two weeks after commencement of therapy, mild pancytopenia was detected by blood count monitoring, with a hemoglobin level of 12.9 g/dL (129 g/L); a mean corpuscular volume of 98.5 µm^3 (98.5 fL); a WBC count of 2,200/µL (2.2 × 10^9/L) with 63% neutrophils (0.63), 27% lymphocytes (0.27), and 10% monocytes (0.10); and a platelet count of 109 × 10^3/µL (109 × 10^9/L). The serum valproate level was 363 µmol/L. Examination of the peripheral blood smear showed no dysplastic features. Examination of the bone marrow aspirate showed
normal cellularity with megaloblastoid erythropoiesis and normal granulopoiesis. Megakaryocytes were adequate in number, with occasional ones showing multiple separate nuclei. Toxic effects of valproate were suspected, and the drug was withheld. His blood cell counts normalized 12 days afterward.

**Discussion**

Valproate is an effective antiepileptic drug. Its use has been extended beyond primary epilepsy to many psychiatric disorders such as acute mania associated with bipolar disorder and schizoaffective diseases. Hematologic toxic effects of valproate vary in type and severity, ranging from marrow failure with fatal aplastic anemia to an incidental finding of RBC macrocytosis. Most reports in the literature were from the pediatric patient group, and thrombocytopenia and RBC macrocytosis were recognized as the most common manifestations of valproate-associated hematologic abnormalities.

The cause for the thrombocytopenia is unclear. Immune-mediated peripheral destruction has been suggested by some authors as the underlying mechanism based on marrow morphologic findings and platelet autoantibody studies. Reports of hematologic toxic effects in adult patients also focused on thrombocytopenia.

More severe side effects of valproate, including aplastic anemia, pure red cell aplasia, and dysmyelopoiesis, have rarely been reported, and all of them were found in pediatric patients. Ganick et al. described 4 children with dysmyelopoiesis who had macrocytosis, Pelger-Huët anomaly, and megakaryocytic dysplasia, similar to our case. Cytogenetic study was not performed in our patients. However, spontaneous hematologic recovery after cessation of valproate therapy was not consistent with a primary myelodysplastic syndrome. Long-term monitoring of platelet counts for a 10-year period in case 1 showed a clear association between valproate therapy and thrombocytopenia. Furthermore, the neutrophil count and hemoglobin level remained normal but dropped precipitously during drug overdose, with accompanying dysmyelopoiesis.

In case 2, in which the valproate level was kept within therapeutic range, the major findings were thrombocytopenia with only mild dysmyelopoiesis. From the observations in our patients and in the literature, it seems that thrombocytopenia is the most sensitive hematologic indicator of the valproate effect, which can occur even when the drug is within therapeutic range.

The drug toxic effects on marrow stem cells, on the other hand, may be more dose-related. In fact, RBC macrocytosis, thrombocytopenia, and the Pelger-Huët anomaly of neutrophils commonly observed in patients receiving valproate therapy can all be manifestations of dysmyelopoiesis. Although we identified only the present 2 adult cases of documented valproate-associated dysmyelopoiesis among our bone marrow records for the past 17 years, the actual prevalence of toxic effects of this particular drug may be higher. Bone marrow study usually is not performed for patients with only mild cytopenias, and marrow dysplasia may be very subtle in such cases. The fact that dysmyelopoiesis can occur years after starting the drug also makes the recognition of an association between valproate and dysmyelopoiesis difficult.

Dysmyelopoiesis associated with valproate therapy occurs in adult as well as in pediatric patients. We postulate that this particular toxic effect may be dose-related and much more common than is recognized. In the elderly patient group, recognition of this association is especially important because these patients are at a higher risk of noncompliance with drug therapy and of drug overdose. Furthermore, when valproate-associated dysmyelopoiesis occurs, it easily can be attributed to a primary myelodysplastic syndrome that also is more prevalent in elderly people. However, unlike valproate-associated dysmyelopoiesis that is fully reversible, primary myelodysplastic syndrome remains an incurable disease in this age group. A correct diagnosis with timely cessation or reduction of valproate treatment not only will minimize the acute morbidity and mortality of severe pancytopenia but also will avoid false prognostication in affected patients.
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From the Department of Pathology, Queen Elizabeth Hospital, Hong Kong, People’s Republic of China.

Address reprint requests to Dr So: Dept of Pathology, Queen Elizabeth Hospital, 30 Gascoigne Rd, Kowloon, Hong Kong, People’s Republic of China.

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