Effect of Valproic Acid on Platelet Count in a Patient with Schizoaffective Disorder

Randy Trinkle

INTRODUCTION

Valproic acid has been used for over 30 years for the treatment of various seizure disorders.[1] After its introduction as an anticonvulsant, valproic acid was also studied for its effectiveness in the management of mood disorders.[2,3] Although fatal hepatic toxicity is the most serious adverse effect associated with valproic acid, this is a rare complication seen primarily in young children receiving polytherapy for epilepsy.[4,5] Hematologic disorders are more common than hepatic necrosis, although detailed studies of the effect of valproic acid on platelet count have been confined almost exclusively to children with seizure disorders.[6-8] There has been only one large-scale pharmacoepidemiological study of adults with mood disorders who were treated with valproic acid monotherapy,[9] and the investigators reported that no patient had a platelet count less than 100 x 10^9/L. Cases of reduced platelet count associated with use of valproic acid to treat mood disorders have only rarely been reported in the psychiatric literature.[10-12] This report describes a middle-aged man with a schizoaffective disorder whose platelet count decreased when valproic acid was started and again when he was challenged with the same drug.

CASE REPORT

A 56-year-old man with a schizoaffective disorder was admitted to a regional psychiatric centre for evaluation and establishment of a suitable therapeutic regimen. He had previously been successfully managed with depot flupenthixol for 4 years, but the depot injections had been stopped 4 months before the admission because of severe tardive dyskinesia. In the month before admission he began appearing in the emergency department describing visitations from angels. His mood was elevated, and he claimed to have important business deals "in the works". At the time, he was employed washing cars at a local auto dealership.

Antipsychotic therapy with risperidone 0.5 mg bid was started on the day of admission. The patient continued to exhibit grandiose behaviour, and valproic acid (at 250 mg daily) was started 24 days after admission. The daily dose was increased to 1000 mg over the next 2 weeks (Figure 1).

Seventeen days after valproic acid was started, a blood sample was drawn for a complete blood count; this was the first blood sample taken since the time of admission. The platelet count had dropped from 214 x 10^9/L (baseline level on admission) to 143 x 10^9/L (normal 130 to 400 x 10^9/L) (Figure 2). Red and white blood cell counts and red blood cell morphology, as well as serum levels of alkaline phosphatase, transaminases, total protein, albumin, and bilirubin, were all normal. Because of the reduced platelet count, valproic acid was discontinued according to a tapering schedule over the next week (Figure 1).

The patient continued to exhibit delusional behaviour, and 6 weeks after admission the antipsychotic drug was changed to olanzapine 5 mg daily. The delusional symptoms abated, but the behaviour of the patient remained grandiose. A month after valproic acid was discontinued, the drug was restarted in combination with lithium. The initial dosage at this time was 500 mg

Figure 1. Dose (solid lines) and serum concentration (solid squares) of valproic acid (VA) since initial admission in a patient with schizoaffective disorder. Reference value for valproic acid: 350 to 700 µmol/L.

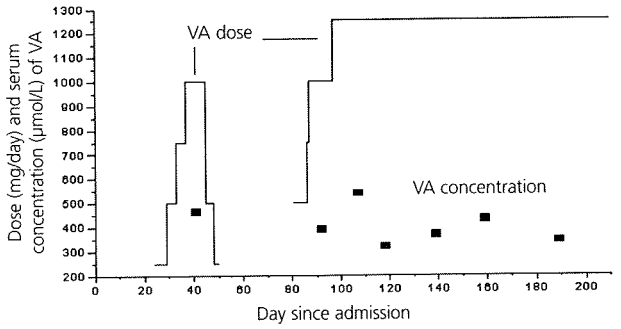
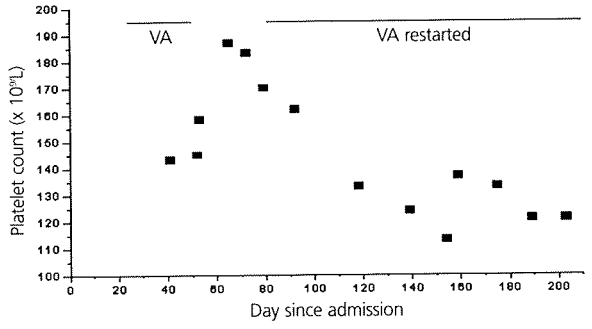


Figure 2. Platelet count since initial admission. The patient's baseline platelet count was 214 x 10^9/L, and the reference value is 130 to 400 x 10^9/L. The solid lines at the top indicate the days on which valproic acid was given.



daily, and the dosage was increased over the next 2 weeks to 1250 mg daily (Figure 1).

The platelet count again decreased after valproic acid was restarted (Figure 2), but the drug was not discontinued. The patient was discharged to a long-term care facility 5 months after admission. At that time, he was receiving olanzapine 5 mg qhs, valproic acid 250 mg bid and 750 mg qhs, and lithium carbonate 300 mg qam and 600 mg qhs. The patient was receiving no other regular medications during his stay in hospital or at discharge.

At no time, either while the patient was in hospital or after discharge, was there any evidence of unusual bleeding episodes, such as epistaxis, bruising, bleeding gums, or hematuria. In addition, there was never any evidence of hepatic dysfunction or hematologic anomaly except the reduced platelet count. The international normalized ratio was measured twice while the patient was in hospital; the values were 1.0 and 1.1 (reference value 0.7 to 1.4) at 99 and 122 days post-admission, respectively.

DISCUSSION

A reduction in platelet count in association with valproic acid therapy for seizure disorders, but not psychiatric disorders, has been reported since the 1970s.[13,14] Detailed studies of this phenomenon, along with other hematologic disorders, have been published only in the last few years, and these have been almost exclusively confined to children.[6-8] The investigators have consistently reported an effect of the serum concentration of valproic acid on the amount of change in platelet count but no unusual bleeding episodes. A single similar study involving 27 adults with a seizure disorder who were receiving valproic acid monotherapy found significantly lower platelet counts in these subjects than in matched controls.[15] Two of the treated patients had platelet counts less than 100 x 10^9/L. Patients treated with valproic acid also had significantly longer bleeding times, although the results of bleeding time tests may not be reproducible because of inter- and intra-operator variability.[16] The percentage of patients who may experience a drop in platelet count of any magnitude cannot be determined from these studies. In 2 studies, 20%[6] and 22%[15] of the patients had a platelet count less than 130 x 10^9/L. On the basis of the limited information available, clinically significant bleeding episodes in patients with a seizure disorder who are receiving valproic acid monotherapy appear rare.

There have been few similar investigations in patients without a seizure disorder. One study of use of valproic acid in 30 adults with movement disorders found that 90% of the patients had a dose-related reduction in platelet count (relative to baseline) and that approximately a third of these had a platelet count less than 145 x 10^9/L.[17] None of the patients were reported to have had any unusual bleeding episodes. In the only study of its kind in psychiatric patients, Tohen and colleagues[9] reported that of nearly 1200 patients (most with a major affective disorder) treated with valproic acid alone, none had a platelet count less than 100 x 10^9/L or suffered any unusual bleeding. No further information about the effect of valproic acid on platelet count was given, and therefore neither the incidence of a decrease in count of any magnitude nor whether this

effect was transitory can be determined from this study, particularly for comparison with people with a seizure disorder. In a comparative study of divalproex and lithium for the treatment of acute mania, Bowden and colleagues[18] reported that as a group, divalproex-treated patients experienced a mean reduction in platelet count of 77 x 10^9/L. None experienced any adverse bleeding or bruising, but the number of patients affected was not given.

A reduction in platelet count associated with valproic acid therapy has only rarely (and recently) been reported in the psychiatric case literature. In one case the only information given was that valproic acid had been discontinued because of the reduced count.[10] In another, a 48-year-old woman with rapid-cycling bipolar disorder suffered a dose-related drop in platelet count (nadir of 45 x 10^9/L while receiving valproic acid 5000 mg/day) but no reported bleeding complications.[12] Only one case of symptomatic thrombocytopenia associated with valproic acid therapy for a psychiatric indication has been reported.[11] A 57-year-old woman with rapid-cycling bipolar disorder presented to an emergency department with extensive upper-extremity bruising. At that time her platelet count was 80 x 10^9/L; she was receiving valproic acid at 1250 mg daily. She had been receiving the drug for 4 years and was known to have dose-dependent thrombocytopenia related to the valproic acid.

Although the mechanism of thrombocytopenia associated with valproic acid is unknown, both a direct effect on platelet production[6] and immune-mediated thrombocytolysis have been proposed.[19] Impairment in platelet aggregation, an additional risk factor for abnormal bleeding, also has been reported.[15] These studies involved patients with seizure disorders. Similar studies of the effect of valproic acid on the platelets of patients with schizophrenia or a mood disorder have not been reported. It is known that platelet phospholipid metabolism,[20,21] incorporation of arachidonic acid,[22,23] and serotonin uptake[24] are altered in patients with various psychiatric disorders, but it is not known whether these changes mean that the effect of valproic acid on platelets would be different for psychiatric patients than for those with a seizure disorder.

It appears that symptomatic thrombocytopenia in psychiatric patients treated with valproic acid monotherapy is rare. Some investigators have found a clear dose- or concentration-dependent relationship,[6-8,15] but others have not.[19] A reduced platelet count also may be a transient effect in some patients.[11,19] The effect may occur within weeks of starting the drug or increasing its dose[11] or it may not occur for years.[12]

Because the consequences of a disturbance in hemostasis can be serious, a baseline platelet count should be obtained before starting valproic acid, and subsequent counts should be taken every 3 or 4 months thereafter. A platelet count also should be taken 3 or 4 weeks after a change in dose. The dose of valproic acid should be decreased if the platelet count drops below 100 x 10^9/L, and the drug should be discontinued if the platelet count does not recover after the dose is reduced. Because a drop in platelet count may be a transient effect, the decision to decrease or discontinue valproic acid could be delayed for 3 to 4 weeks if there is no evidence of unusual bleeding. Although the evidence for a relationship between valproic acid concentration and platelet count in this population is scanty, it would be prudent to assume that the risk of thrombocytopenia probably increases with an increase in dose, as it does in patients being treated for a seizure disorder. Finally, the patient should be advised to seek medical attention if he or she experiences hematuria, epistaxis, or any other unusual bleeding.

References

1. Rall TW, Schleifer LS. Drugs effective in the therapy of the epilepsies. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. *The pharmacological basis of therapeutics.* New York: Pergamon Press; 1991. p. 436-62.
2. Guay DR. The emerging role of valproate in bipolar disorder and other psychiatric disorders. *Pharmacotherapy* 1995;15: 631-47.
3. Keck PE Jr, McElroy SL, Strakowski SM. New developments in the pharmacologic treatment of schizoaffective disorder. *J Clin Psychiatry* 1996;57(Suppl 9):41-8.
4. Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. *Neurology* 1987;37:379-85.
5. Bryant AE 3rd, Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. *Neurology* 1996;46:465-9.
6. May RB, Sunder TR. Hematologic manifestations of long-term valproate therapy. *Epilepsia* 1993;34:1098-101.
7. Allarakhia IN, Garofalo EA, Komarynski MA, Robertson PL. Valproic acid and thrombocytopenia in children: a case-controlled retrospective study. *Pediatr Neurol* 1996;14:303-7.
8. Hauser E, Seidl R, Freilinger M, Male C, Herkner K. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. *Brain Dev* 1996;18:105-9.
9. Tohen M, Castillo J, Baldessarini RJ, Zarate C Jr, Kando JC. Blood dyscrasias with carbamazepine and valproate: a pharmacoepidemiological study of 2,228 patients at risk. *Am J Psychiatry* 1995;152:413-18.
10. Ravindran AV, Jones BW, Al-Zaid K, Lapierre YD. Effective treatment of mania with olanzapine: 2 case reports [letter]. *J Psychiatry Neurosci* 1997;22:345-6.

11. Kaufman KR, Gerner R. Dose-dependent valproic acid and thrombocytopenia in bipolar disorder. *Ann Clin Psychiatry* 1998;10:35-7.

12. Fawcett RG. Dose-related thrombocytopenia and macrocytic anemia associated with valproate use in bipolar disorder [letter]. *J Clin Psychiatry* 1997;58:125.

13. Winfield DA, Benton P, Espir ML, Arthur LJ. Sodium valproate and thrombocytopenia. *BMJ* 1976;2:981.

14. Raworth RE, Birchall G. Sodium valproate and platelet count [letter]. *Lancet* 1978;1:670-1.

15. Gidal B, Spencer N, Maly M, Pitterle M, Williams E, Collins M, et al. Valproate-mediated disturbances of hemostasis: relationship to dose and plasma concentration. *Neurology* 1994;44: 1418-22.

16. Bontempo FA. Use and misuse of the bleeding time. *Transfus Med Update* [serial online]. 1994 Apr. Available at: URL: http://www.itxm.org/Archive/tmu4-94.htm (1999 July 16).

17. Neophytides AN, Nutt JG, Lodish JR. Thrombocytopenia associated with sodium valproate treatment. *Ann Neurol* 1979;5:389-90.

18. Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. *JAMA* 1994;271:918-24.

19. Barr RD, Copeland SA, Stockwell ML, Morris N, Kelton JC. Valproic acid and immune thrombocytopenia. *Arch Dis Child* 1982;57:681-4.

20. Demisch L, Heinz K, Gerbaldo H, Kirsten R. Increased concentrations of phosphatidylinositol (PI) and decreased esterification of arachidonic acid into phospholipids in platelets from patients with schizoaffective disorders or atypic phasic psychoses. *Prostaglandins Leukot Essent Fatty Acids* 1992;46: 47-52.

21. Ripova D, Strunecka A, Nemvoca V, Farska I. Phospholipids and calcium alterations in platelets of schizophrenic patients. *Physiol Res* 1997;46:59-68.

22. Yao JK, van Kammen DP, Gurklis JA. Abnormal incorporation of arachidonic acid into platelets of drug-free patients with schizophrenia. *Psychiatry Res* 1996;60:11-21.

23. Demisch L, Gerbaldo H, Gebhart P, Georgi K, Bochnik HJ. Incorporation of 14C-arachidonic acid into platelet phospholipids of untreated patients with schizophreniform or schizophrenic disorders. *Psychiatry Res* 1987;22:275-82.

24. Meltzer HY, Arora RC, Baber R, Tricou BJ. Serotonin uptake in blood platelets of psychiatric patients. *Arch Gen Psychiatry* 1981;38:1322-6.

Randy Trinkle, BScPharm, BA, was, at the time this case occurred, a Staff Pharmacist, Pharmacy Department, Dawson Creek and District Hospital, Dawson Creek, BC. He is currently a Clinical Pharmacist, Pharmacy Department, Prince Rupert Regional Hospital, Prince Rupert, BC.

Address correspondence to:
Randy Trinkle
Clinical Pharmacist
Pharmacy Department
Prince Rupert Regional Hospital
1305 Summit Avenue
Prince Rupert BC
V8J 2A6
e-mail: rtrinkle@mail.citytel.net