



Incidences of Thrombocytopenia in Psychiatric Population Taking Valproic Acid: Demand's Clarification and Attention

Augustin Kumar Bharti*

Department of Pharmacology, Pt. J. N. M. Medical College, Raipur, 492001, India.

*Corresponding author's E-mail: akrbharti@gmail.com

Accepted on: 10-06-2014; Finalized on: 30-06-2014.

ABSTRACT

Valproic acid (VPA) has been used with increasing frequency for the treatment of many psychiatric conditions, in patients. There have been wide-ranging reports of thrombocytopenia and other forms of platelet dysfunction as side effects of valproate therapy, but the exact incidence is not known clear yet, Therefore in these review are trying to accumulate the evidences focus on prevalence of thrombocytopenia in psychiatric population receiving VPA and to identify potential risk factors for a patient to develop thrombocytopenia while taking VPA. Our findings underline the importance of monitoring platelet counts in patients treated with VPA, as advised in the product label, before the onset, and during the therapy. This monitoring should be continued indefinitely at least on a quarterly basis. More vigilant monitoring of platelet levels should occur in the elderly, and above all in patients receiving high dosages because platelet abnormalities are seem to be dose-related.

Keywords: Valproic Acid, Thrombocytopenia, Psychiatric conditions.

INTRODUCTION

Many haematological disorders may be encountered in psychiatric practice. Almost all classes of psychotropic agents have been reported to cause blood dyscrasias. These include deficiencies in various constituents—leucopenia, neutropenia, agranulocytosis, thrombocytopenia, anaemia—and leucocytosis, thrombocytosis, eosinophilia and altered platelet function. The main, the mechanisms underlying these disorders are poorly understood. Recent reviews of the subject are available.¹⁻³

Valproic acid (VPA) has been used with increasing frequency for the treatment of many psychiatric conditions⁴ including those in elderly patients.⁵

The therapeutic benefits of valproate in psychiatric conditions are most substantially recognized in bipolar disorder. However, this well tolerated medication may be beneficial in the treatment of other mental illness like: - depressions, anxiety and psychotic disorder.

There have been wide range of accumulated reports of thrombocytopenia and other forms of platelet dysfunction as side effect of valproate therapy^{23, 28, 30} but as exact incidence is poorly understand. The focus of this review will be on incidences of thrombocytopenia events in psychiatric population taking VPA for psychiatric indications.

VALPROIC ACID

Valproic acid (VPA, 2-propylpentanoic acid), a short branched chain fatty acid, was originally synthesized as an analog of valeric acid extracted from *Valeriana officinalis*. It has been used worldwide for decades, in the form of sodium valproate, as an antiepileptic drug with therapeutic value for absence, partial and tonic-clonic

seizures.^{6, 25-26} Valproates is believed to affect the function of the neurotransmitter GABA in the human brain, making it an alternative to lithium salts in treatment of bipolar disorder. Its mechanism of action includes enhanced neurotransmission of GABA (by inhibiting GABA- transaminase, which breaks down GABA). However, several other mechanisms of action in neuropsychiatric disorders have been proposed for valproic acid in recent year.⁷ Valproic acid also blocks the voltage-gated sodium channels and T-type calcium channels. These mechanisms make valproic acid a broad-spectrum anticonvulsant drug. Valproic acid is an inhibitor of the enzyme histone deacetylase-1 (HDAC1), hence it is a histone deacetylase inhibitor. Various studies have been conducted to evaluate the valproate induced thrombocytopenia in different group of patient.

Table 1: Haematological disorder of some mood stabilising agents

Drugs	Effects
Carbamazepine	Agranulocytosis, anaemia, eosinophilia, leucocytosis, leucopenia, pure erythrocyte aplasia, thrombocytopenia
Gabapentin	Leucopenia
Lamotrigine	Anaemia, pancytopenia, pure erythrocyte aplasia, thrombocytopenia
Lithium	Leucocytosis, leukaemia, thrombocytosis
Valproate	Anaemia, neutropenia, pure erythrocyte aplasia, thrombocytopenia

Thrombocytopenia is the result of falling the number of platelet from 150,000/microL. There are three main reasons of thrombocytopenia, (a)-Decreasing of making platelet (b)-Increasing of destruction platelet (c)-Changing of distribution platelet. Thrombocytopenia separates



three stages as numerical. Mild: 100,000 - 150,000/microL, Moderate: 50,000 - 100,000/microL. Severe: < 50,000/microL. However, thrombocytopenia is not usually detected clinically until the platelet count has fallen to levels below 100,000/microL.

Table 2: Classification of Thrombocytopenia

1. Artificial thrombocytopenia
a. Forming of platelet which relevant to anticoagulant immunoglobulin (pseudo thrombocytopenia)
b. Platelet satellitism
c. Giant platelets
2. Decreased product thrombocyte
a. Megakaryocyte hypoplasia or suppression
b. Ineffective thrombopoiesis
c. Defeat in mechanism which are controlling thrombopoiesis
d. Hereditary thrombocytopenia
3. Increased platelet destruction
a. Immunologic
- Autoimmune
- Primary (Immune thrombocytopenia)
- Secondary (Infections, pregnancy, collagen tissue diseases, lymph proliferative diseases, drugs)
- Alloimmune
- Neonatal thrombocytopenia
- Post-transfusion purpura
b. Nonimmunologic
- Thrombotic microangiopathies
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Haemolytic-uremic syndrome
- Abnormal vascular relevant to the surface of thrombocytopenia
- Others (infection, massif blood transfusion)
4. Abnormal platelet distribution
a. The disease that capture spleen (neoplasia, congestive, infiltration)
b. Hypothermia

How the drug-induced thrombocytopenias occur?

Drug-induced thrombocytopenia was first described in the 19th century, yet our understanding of its pathogenesis continues to evolve. The list of drugs implicated in drug induced thrombocytopenia is extensive and growing. Many, if not most, of these medications induce thrombocytopenia by immune mechanisms.²² Because the degree of thrombocytopenia can put patients at risk for serious bleeding, a prompt diagnosis is key to clinical management.⁸

In fact, the pathophysiologic mechanisms of Drug-induced thrombocytopenia are diverse but can be split into two major categories: (1) Decreased platelet production via marrow suppression and (2) Peripheral platelet clearance, usually by one of several possible immune mechanisms.^{9-11, 27}

Thrombocytopenia occurs in different mechanism. Although some drugs causes the bone marrow suppression or pressuring the megakaryocyte in producing thrombocytopenia.^{27, 29} Some drugs directly affect platelet. In most of the drugs there has been thrombocytopenia with antibody in some of the sensitive people. The drugs which are used in cancer treatment and also caused bone marrow suppression are cytostatic. These drugs suppress bone marrow and cause pancytopenia, Busulfan, melphalan, etoposide cyclophosphamide, folic acid antagonists, antimetotics, and cytostatic antibiotics can cause thrombocytopenia by suppressing megakaryocyte. Immunological thrombocytopenia occurs in ways that drugs quinine, quinidine, phenacetin, methicillin, penicillin, sulphonamides, gold salts, and drugs such as heparin. These drugs which accurs some of the antibodies with platelets complement reason fixing. Result of this platelets turns into destruction and developed thrombocytopenia.

Table 3: Mechanisms of Immune-Mediated Drug-Induced Thrombocytopenia

Mechanism	Description	Clinical Consequence	Special Laboratory Testing*	Prototype Drugs
Hapten-dependent	Drug (hapten) binds covalently to platelet membrane glycoprotein producing a neoepitope recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Penicillin, cephalosporins
Drug-glycoprotein complex (quinine-type)	Drug interacts noncovalently with platelet membrane glycoprotein; antibody binds to drug-glycoprotein complex	Hemorrhage	Drug-dependent platelet antibody assay	Quinine, quinidine, NSAIDs†, sulfonamides
Ligand-induced binding site (fiban-type)	Drug binds to platelet GPIIb/IIIa complex inducing conformational change elsewhere and formation of a neoepitope recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Eptifibatide, tirofiban, Icatrafiban
Drug-specific antibody	Drug consists of chimeric Fab fragments against GPIIb/IIIa with a murine component that is recognized by antibody	Hemorrhage	Drug-dependent platelet antibody assay	Abciximab
Autoantibody	Drug induces an autoantibody that reacts with a platelet surface glycoprotein in the absence of the drug	Hemorrhage	Anti-platelet antibody assay (nonspecific)	Gold salts, procainamide
Immune complex	Drug reacts with platelet factor 4 to produce an antigenic complex against which antibodies react; resulting immune complexes bind to platelet Fc receptors resulting in platelet activation	Thrombosis	Heparin-platelet factor 4 antibody assay	Unfractionated heparin, low-molecular-weight heparins

* See text for details regarding testing modalities.

† NSAIDs indicates nonsteroidal anti-inflammatory drugs.



The immune thrombocytopenia depends on drugs occurs in three mechanism,

i) **The type of kinidin:** The antibody occurs when the drug is taken for the first time. This antibody, when the drug is taken second time, it takes out complexity with drug, this complexity which connecting platelet's membrane causes platelets go away from the circulation;

ii) **The type of penicillin:** The drug connects directly to the platelet membrane and it causes leaving the platelets rapidly from the circulation;

iii) **The type of heparin:** Heparin creates a complex with platelet factor- 4 (TF4) which is forming from the platelet's alpha granule is a cationic protein. The antibodies which are developed against to this complex Immunoglobulin G (IgG) connect complex heparin TF4 on platelet cell membrane, endothelia cell membrane in plasma and then cause releasing platelet, thrombosis and decreasing platelet counts.¹² The drugs which cause thrombocytopenia are shown in Table 1.

Incidences of valproic acid induced thrombocytopenia

Valproic acid (N-dipropylacetic acid) or valproate (VPA) is a structurally unrelated to any other anti epileptic drug. Valproic acid (VPA) is a commonly used antiepileptic drug. It is widely used as a first-line agent for patients with partial or generalised epilepsy. Thrombocytopenia is one of the most common side effects associated with VPA therapy, with incidences ranging from 1% to 30%.¹³⁻¹⁴ Thrombocytopenias has been reported in 6% - 33% of adult patient with epilepsy taking valproate, but a lowering of platelet count was seen in almost all patients and appeared to be dose related.¹⁵

It is mild and transient in most cases and usually resolves spontaneously on dosage reduction or withdrawal of the^{14, 16} have demonstrated that the platelet count decreases at high serum VPA levels.^{14, 16} The platelet count has also been shown to be inversely correlated to VPA dose and plasma VPA concentration.^{14, 17}

Reports on the use of valproate with psychiatric patients have described a drop in platelet count without thrombocytopenia or with a minimal incidence of thrombocytopenia¹⁸⁻¹⁹ and without any associated adverse clinical events related to these findings. The perceived novelty and under recognition of the platelet-lowering effects of valproate is illustrated by case reports of thrombocytopenia associated with valproate in psychiatric populations.²⁰

Accumulated reports suggested that, various studies have been conducted to evaluate the valproate induced thrombocytopenia in different group of patient.

A study on 30 patients on sodium valproate with daily doses of 1,200 to 3,000 mg in which the significant reduction of the platelet count was observed. They have thrombocytopenia without any concomitant bleeding

abnormalities occurred in 10 of the patients where else platelet counts returned to baseline levels after withdrawal of the drug.²¹

Platelets count in VPA patients

A normal platelet count is between 150,000 and 450,000 platelets per microliter (one-millionth of a liter, abbreviated mL). The average platelet count is 237,000 per mL in men and 266,000 per mL in women.

A platelet count below 150,000 per mL is called thrombocytopenia, while a platelet count over 450,000 is called thrombocytosis. Platelets seem to have a large backup capacity: blood typically still clots normally as long as the platelet count is above 50,000 per mL (assuming no other problems are present). Spontaneous bleeding doesn't usually occur unless the platelet count falls to 10,000 or 20,000 per mL. Thrombocytopenia was defined as mild, platelet count of $101-150 \times 10^3/\text{mm}^3$; moderate, platelet count of $40-100 \times 10^3/\text{mm}^3$; or severe, platelet count less than $40 \times 10^3/\text{mm}^3$.

Administration of VPA at our psychiatric hospital has increased substantially over the past 5 years, and we have observed a corresponding increase in the number of reports of thrombocytopenia and we developed a further hypothesis that the platelet-lowering effects of valproate are increased in elderly patients. If these hypotheses are true, more careful monitoring than is currently suggested in the psychiatric literature is warranted, especially in the treatment of elderly patients, who are at increased risk for medical comorbidity, polypharmacy, and traumatic falls. There are few published analyses of blood dyscrasias related to VPA in patients with psychiatric disorders.

Therefore these evidences focus on prevalence of thrombocytopenia in hospital psychiatric population receiving VPA and to identify potential risk factors for a patient to develop thrombocytopenia while taking VPA.²⁴

Mechanism underlying valproic acid induced haematological changes during psychiatric treatment

Drug induced thrombocytopenia may occur as a result of suppression of platelets production and immune mechanism. The sciences behind the valproic acid induced haematological changes are lacking and stand still not enough.

CONCLUSIONS AND FUTURE DIRECTIONS

Thrombocytopenia is one of the commonest side effect associated with valproate therapy however, the exact mechanism of valproate associated thrombocytopenia is unclear.

Since valproic acid is very commonly used drug for various psychiatric illness. It is important to keep one updated with the knowledge of adverse effect of valproic acid. Therefore, there is need of exploration study, which will open new vista for valproate associated thrombocytopenia.



In conclusion we state that future studies will need to underline the importance of monitoring platelet counts on patients treated with VPA, as advised in the product label, before the onset and during the therapy.

REFERENCES

- Duggal HS, Singh I, Psychotropic drug-induced neutropenia, *Drugs Today (Barc)*, 41(8), 2005, 517-26.
- Hall RL, Smith AG, Edwards JG, Haematological safety of antipsychotic drugs, *Expert Opinion Drug Saf*, 2, 2003, 395-399.
- Oyesanmi O, Kunkel EJ, Monti DA, Field HL, Hematologic side effects of psychotropics, *Psychosomatics*, 40, 1999, 414-421.
- McElroy SL, Keck PE Jr, Pope HG Jr, Hudson JI, Valproate in psychiatric disorders: literature review and clinical guidelines, *J Clin Psychiatry*, 50 (suppl 3) 1989, 23-29.
- Risinger RC, Risby ED, Risch SC. Safety and efficacy of divalproex sodium in elderly bipolar patients, *J Clin Psychiatry*, 55, 1994, 215.
- Loescher V, Basic pharmacology of valproate, A review after 35 years of clinical use for the treatment of epilepsy, *CNS Drugs*, 16, 2002, 669-694.
- Rosenberg G, The mechanisms of action of valproate in neuropsychiatric disorders: can we see the forest for the trees? *Cellular and Molecular Life Sciences*, 64 (16), 2007, 2090-103.
- Barton Kenney, Gary Stack, Drug-induced thrombocytopenia, *Archives of pathology & laboratory medicine*, 133(2), 2009, 309-14.
- Visentin GP, Liu CY, Drug-induced thrombocytopenia, *Hematol Oncol Clin North Am*, 21, 2007, 685-696.
- Patnode NM, Gandhi PJ, Drug-induced thrombocytopenia in the coronary care unit, *J Thromb Thrombolysis*, 10, 2000, 155-167.
- Hillman RS, Ault KA, Rinder HM, *Hematology in Clinical Practice*. New York, NY: McGraw Hill, 2005.
- George JN, Rizvi MA, Thrombocytopenia, Eds: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn A. *Williams Hematology*. 6th (Ed.) New York: McGraw-Hill Co. press; 2001, 1495-1539.
- Smith FR, Boots M, Sodium valproate and bone marrow suppression, *Ann Neurol* 1980; 8:197-9.
- May RB, Sunder TR, Haematological manifestations of long-term valproate therapy, *Epilepsia*, 34, 1993, 1098-101.
- Covanis A, Gupta AK, Jeavons PM, Sodium valproate: monotherapy and polytherapy, *Epilepsia*, 23, 1982, 693-720.
- Delgado MR, Riela AR, Mills J, Browne R, Roach S, Thrombo-cytopenia secondary to high valproate levels in children with epilepsy, *J Child Neurol*, 9, 1994, 311-4.
- Eastham RD, Jancar J, Sodium valproate and platelet counts, *Br Med J* 1980, 280:186
- Calabrese JR, Markovitz PJ, Kimmel SE, Wagner SC, Spectrum of efficacy of valproate in 78 rapid-cycling bipolar patients, *J Clin Psychopharmacol*, 12 (suppl 1), 1992, 53S-56S.
- Tohen M, Castillo J, Baldessarini RJ, Zarate C Jr, Kando JC, Blood dyscrasias with carbamazepine and valproate: a pharmaco epidemiological study of 2,228 patients at risk, *Am J Psychiatry*, 152, 1995, 413-418.
- Kaufman KR, Gerner R, Dose-dependent valproic acid thrombocytopenia in bipolar disorder, *Ann Clin Psychiatry*, 10, 1998, 35-37
- Winfield DA, Benton P, Espri MLE, Arthur LJH. Sodium valproate and thrombocytopenia. *Br Med J*, 2, 1976, 981.
- Barr RD, Copeland SA, Stockwell ML, et al. Valproic acid and immune thrombocytopenia. *Arch Dis Child*, 57, 1982, 681-684.
- Sandler P M, Bevan P C, Roberts G E, et al. Interaction between sodium valproate and platelets: a further study, *Br Med J*, II, 1979, 1476.
- Conley E L, Coley KC, Pollock BG, Dapos SV, Maxwell R, Branch RA. Prevalence and risk of thrombocytopenia with valproic acid: experience at a psychiatric teaching hospital, *Pharmacotherapy*, 21(11), 2001, 1325-30.
- Sachs GS, Printz DJ, Kahn DA, et al. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med*, 76 (Apr, special issue) 2000, 1-104.
- Balfour JA, Bryson HM, Valproic acid: A review of its pharmacology and therapeutic potential in indications other than epilepsy, *CNS Drugs*, 2, 1994, 144-173.
- Smith FR, Boots M, Sodium valproate and bone marrow suppression, *Ann Neurol*, 1980; 8: 197-199.
- Finsterer J, Pelzl G, Hess B. Severe, isolated thrombocytopenia under polytherapy with carbamazepine and valproate, *Psychiatry Clin Neurosci*, 55(4), 2001, 423-426.
- Kishi T, Fujita N, Kawaguchi H, et al. Bone marrow suppression induced by high dose valproic acid. *Arch Dis Child*, 71, 1994, 153-155.
- Rochel M, Ehrental W, Haematological side effects of valproic acid, In: Oxley J, Janz D, Meinardi H, (Ed.) *Antiepileptic Therapy: Chronic Toxicity of Antiepileptic Drugs*. New York, Raven Press, 1993, 101-103.

Source of Support: Nil, Conflict of Interest: None.

