Epilepsy Journal
ISSN: 2472-0895

Knežević-Pogančev, J Epilepsy 2016, 2:1
http://dx.doi.org/10.4172/2472-0895.1000e106

Editorial Open Access

# Valproic Acid Induced Isolated Thrombocytopenia after Acute Respiratory Infection

**Marija Knežević-Pogančev***

*Child and Youth Health Care Institute of Vojvodina, School of Medicine, University of Novi Sad, Serbia*

**Abstract**

Valproic acid is the most used antiepileptic drug in children. Thrombocytopenia is one of known adverse effects of valproic acid. Acute respiratory infections are the most frequent acute infections in children.

We present eleven cases of resistant thrombocytopenia in children on valproic acid therapy within therapeutic levels. Thrombocytopenia (without clinical signs) appeared after a short febrile episodes and signs and symptoms of acute respiratory infection, presenting with only few petehial skin spots. It does not respond to intravenous immunoglobulin's, nether to corticosteroids. Thrombocytopenia responded dramatically to withdrawing of valproic acid.

Complete platelet normalization after valproic acid withdrawal proved known adverse drug reaction between valproic acid and the thrombocytopenia this association.

**Keywords:** Valproic acid; Thrombocytopenia; Children; Anticonvulsant drugs; Hematological

## Introduction

Thrombocytopenia is a condition in which the blood has a lower than normal (150-450 g/l) platelet count (PLT). Risk of mild bleeding occurs only when the PLT count falls below 50 g/l. The risk of serious bleeding occurs when the level is below 20 g/l) [1]. Valproic acid (VPA), the most often used anticonvulsant in children, belongs to a group of anticonvulsant drugs effective in controlling a wide variety of seizures. VPA can cause hematological and liver toxicity, which is usually blood level dependent [2,3]. Drug-induced thrombocytopenia can be caused by certain drugs in sensitive people by producing drug-dependent antibodies that destroying PLT [4]. VPA associated thrombocytopenia has been reported ranging from 1 to 21% but, severe clinically significant thrombocytopenia is rare. During viral infection or acute febrile illness, such reaction may occur even with normal blood levels [5]. This should be anticipated in children on valproic acid with acute respiratory infections [6,7].

Platelet count can be normalized by withdrawing the drug, and the identification of the responsible drug is important to prevent reexposure. A causal relationship between rising plasma VPA levels and reduced platelet counts, with additional risk factors including female gender and lower baseline platelet counts [8].

## Case Report

We report eleven children on VPA immunotherapy developing resistant thrombocytopenia, without clinical signs, after acute respiratory infections with prompt platelet normalization after withdrawing VPA. All the patients have been treated in Institute for child and youth health care of Vojvodina in period 01.09.1992-01.09.2015. Inform consent for data presenting was signed from patients parents. Study variables included patient age, most recent platelet count, VPA dose, dose/kg, and serum level (Tables 1 and 2).

## Discussion

The mechanism of VPA-induced thrombocytopenia in our patients is unclear. The most common is the VPA concentration-dependent thrombocytopenia presence of high VPA serum levels. The probability of developing thrombocytopenia substantially increased at trough VPA levels above 100 μg/ml in women and above 130 μg/ml in men, with additional risk factors including female gender and lower baseline platelet counts [8]. Serum levels of our patients were in lower third of therapeutic levels. VPA has antiplatelet activity, reduces sCD40L levels in plasma and in washed human platelets, platelet activating factor-induced activation of glycogen syntheses kinase 3β in platelets in a manner that alters sCD40L release from platelets [9]. Interval between the initiation of VPA introduction and PLT decrease is variable, ranging from 8 days to 16 months [2]. The mean time from VPA exposure to the first observed episode of thrombocytopenia in our patients was 612 days (range 612-1211), but it was during first 3 days of respiratory infection, in second and third day of febrile state. Women are described to be more likely to develop thrombocytopenia compared to men with females at approximately twice the risk. In our group there was no significant gender difference (6 boys: 5 girls). Negative diagnostic work up and resistant thrombocytopenia which responded remarkably to VPA withdrawal suggested drug adverse reaction in our patients.

## Conclusion

Need to consider valproate drug toxicity in the differentials for thrombocytopenia even in children with clinical presentations that may be more suggestive of an infective etiology is emphasized. In all children using VPA, the platelet count should be monitored during respiratory infections.

***Corresponding author:** Marija Knežević-Pogančev, Child and youth health care Institute of Vojvodina, School of medicine, University of Novi Sad, Serbia, Tel: 381 63 7789285; E-mail: mkp.marija@gmail.com

**Received** January 25, 2016; **Accepted** January 27, 2016; **Published** February 07, 2016

**Citation:** Knežević-Pogančev M (2016) Valproic Acid Induced Isolated Thrombocytopenia after Acute Respiratory Infection. J Epilepsy 2: e106. doi:10.4172/2472-0895.1000e106

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 0-18years | Proved hematology or immunology disease |
| Epilepsy therapy longer than 18 months | Suspect hematology or immunology disease |
| Valproic acid therapy at list 18 months | Previous observed low PLT |
| Five normal PLT findings before this episode | Over therapeutic VPA serum level |
| Excluded other hematology diseases | Medication other than VPA and antipyretic |
| | Clinical sign of thrombocytopenia |

**Table 1:** Inclusion/exclusion criteria.

| Characteristics | Case |
|---|---|
| Age (months) | 34 |
| Day of VPA therapy | 712 (630-1117) |
| VPA dose mg/kg/day | 21.57 (19.1-25.1) |
| VPA serum level (mocrog/l) | 450.1 (356-589) |
| Thrombocytopenia appearance - disease day | 3 (2-5) |
| Co-medication (ibuprofen) | 5 |
| Co-medication (paracetamol) | 1 |
| Co-medicatin (ibuprofen+paracetamol) | 6 |
| Viral immunology tests/ negative | 10 |
| Influenza A – increased IgM | 1 |
| Initial PLT (G/l) | 54 ( 23-98) |
| Lowest PLT (G/l) | 27.3 (18-37) |
| Cortico therapy | 9 |
| Intravenous immunoglobulin therapy | 3 |
| VPA withdrawal day | 5.3 (2-11) |
| Day to normalization after VPA withdrawal | 5 (3-9) |

**Table 2**: Characteristics of patients with thrombocytopenia.

## References

1. National Heart Lung Blood Institute. Thrombocytopenia, USA.
2. Abdallah C (2013) Valproic acid and acquired coagulopathy. Paediatr Anaesth 23: 674-675.
3. Weiner D, Nir V, Klein-Kremer A, Kassem E (2013) Chronic valproic acid intoxication. Pediatr Emerg Care 29: 756-757.
4. Nerumalla CS, Shah AS (2013) A Case of Thrombocytopenia Associated With Valproic Acid Treatment Prim Care Companion CNS Disord 15: PCC.13l01526.
5. Vasudev K, Keown P, Gibb I (2010) Hematological effects of valproate in psychiatric patients: what are the risk factors? J Clin Psychopharmacol 30: 282–285.
6. Verrotti A, Scaparrotta A, Grosso S, Chiarelli F, Coppola G (2014) Anticonvulsant drugs and hematological disease. Neurol Sci 35: 983-993.
7. Zighetti ML, Fontana G, Lussana F, Chiesa V, Vignoli A, et al. (2015) Effects of chronic administration of valproic acid to epileptic pat.ients on coagulation tests and primary hemostasis. Epilepsia 56: e49-e52.
8. Nasreddine W, Beydoun A (2008) Valproate-induced thrombocytopenia: a prospective monotherapy study. Epilepsia 49: 438-445.
9. Davidson DC, Hirshman MP, Spineli SL, (2011) Antiplatelet activity of valproic acid contributes to decreased soluble CD40 ligand production in HIV type 1-infected individuals. J Immunol 186: 584-591.

**Citation:** Knežević-Pogančev M (2016) Valproic Acid Induced Isolated Thrombocytopenia after Acute Respiratory Infection. J Epilepsy 2: e106. doi:10.4172/2472-0895.1000e106