

# Valproic acid-associated pancytopenia: A dose-dependent adverse effect

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## ABSTRACT

Pancytopenia (PCP) is a life-threatening condition which is rarely associated with valproic acid (VPA). We present a case of an adult female with epilepsy that was seizure-free for the last three years. She was in use of VPA 500 mg bid. The subject reported that she recently had new seizures. VPA dose was increased to 500mg tid. One-month later, she was asymptomatic and seizure-free. Laboratory tests showed PCP. VPA dose was decreased to 500mg bid and maintained. One-month later, the complete blood cell count was normal. After one-year, the patient reported new episodes of convulsion. VPA was increased to 500 mg tid. One-month later, the laboratory tests revealed PCP. Valproic acid was discontinued. Carbamazepine 200 mg tid was started. After two-months, the laboratory tests were normal. The subject was seizure-free and asymptomatic for the last year.

**Keywords:** valproic acid, pancytopenia, epilepsy

## INTRODUCTION

Valproic acid (VPA), or valproate, is a fatty acid derivative and was originally synthesized in 1881 by Beverly S. Burton. It received approval in 1978 from the Food and Drug Administration to be used as an antiepileptic drug (1). Because of its proven therapeutic benefits, low cost, and presumably, no abuse potential, VPA is widely used in the management of several neurological disorders.

Pancytopenia is a life-threatening condition which is rarely associated with VPA. To the authors' knowledge, there is only one case of VPA rechallenge after VPA-associated pancytopenia that has been reported in the literature (2).

Herein, we report a case of an adult female diagnosed with epilepsy, in which VPA was increased due to uncontrolled seizures. Weeks after, laboratory tests showed pancytopenia; then, the medication dose was decreased and the hematologic abnormalities had full resolution. Several months later, the attempt to increase VPA resulted in a decrease in all blood cell lineages.

## CASE REPORT

A 38-year-old female with secondary epilepsy due to traumatic brain injury was seizure-free for the last three years. She was in use of VPA 500 mg twice a day. But during a routine visit, the subject reported new seizures that started within the last three months. The ictal episodes were of focal onset with impaired awareness and progression to bilateral tonic-clonic involvement according to her description. Her comorbid condition was hypothyroidism, which was effectively treated with levothyroxine 50 mcg. The neurological examination was normal. Laboratory tests were within normal limits (Table 1 – T1). The VPA dose was increased to 500 mg three times daily.

One month later, she was asymptomatic and seizure-free. Laboratory tests showed pancytopenia (Table 1 – T2). The serum levels of vitamin b12, homocysteine, and folate were normal. The subject worked in agriculture and her family history was negative for hematological diseases. The review of systems was negative for fatigue, fevers, head-

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*Article History:*

Received: 11 August 2019

Accepted: 25 August 2019

**TABLE 1.** Laboratory blood tests according to valproic acid dose along time

Time (T)	T1	T2	T3	T4	T5	
Valproic acid dose	1,0 g	1,5g	1g	1,5g	1g	
Parameter(normal)	Hemoglobin (12-16 g/dl)	13,9	9,8	13	9,6	14
	Neutrophils (>1,800/microL)	2600	1600	2489	1320	2795
	Platelet (>150,000 /microL)	218,000	83,000	145,000	87,000	160,000
	Valproic acid (50-100 mg/l)	–	63,4	–	70	–

aches, paresthesias, weakness, weight change, acute viral or other intercurrent illness. The physical examination was normal. The VPA dose was decreased to 500 mg twice a day and maintained at this dosage due to financial reasons. A month later, the complete blood cell count was normal.

After one year, the patient reported new episodes of convulsion. Laboratory tests were normal (Table 1 – T3). The neurological exam was normal. Due to socioeconomic reasons, the therapy with VPA was optimized and the dose was increased to 500mg three times a day. One month later, the laboratory tests showed pancytopenia (Table 1 – T4). Valproic acid was decreased to 500 mg twice a day and subsequently discontinued. Carbamazepine 200 mg three times daily was started. After two months, the laboratory tests were normal (Table 1 – T5). The subject was seizure-free and asymptomatic for the last year.

## DISCUSSION

Epilepsy is characterized by chronically abnormal brain activity, with unprovoked (or reflex) seizures and a probability of their recurrence (1). In this context, valproic acid (VPA) is a medication commonly used in the management of this disorder. It is considered a broad-spectrum antiepileptic drug since it has been successfully used to treat almost all types of seizures (1). The probable main mechanism of action of VPA is related to  $\gamma$ -aminobutyric acid, in which VPA potentiates the transmission, increases synthesis, decreases turnover, and inhibits the degradation of this neurotransmitter (3). Also, VPA was already reported to be associated with other channels such as NMDA, calcium, potassium, and sodium (1,3).

The several pathways related to VPA can explain its broad-spectrum of action in epilepsy and its effectiveness in the treatment of other diseases, such as mood disorders and migraine (1). However, this is also likely to account for the drug's many adverse effects. In this way, VPA hematological side effects are frequent, and among these, the thrombocytopenia and macrocytosis are the most common (4). Pancytopenia is a less commonly reported adverse effect, but it is a life-threatening condition and fatalities have been described (4,5).

VPA rechallenge after VPA-associated pancytopenia was rarely reported in the literature. We identified only one case report published in English and we compared it with the present case (Table 2) (2). A literature search was performed in Embase, Google Scholar, Lilacs, Medline, Scielo, and ScienceDirect, on a set of terms that included pancytopenia, valproic acid, and valproate.

In the cases of Table 2, both subjects were diagnosed with pancytopenia from routine laboratorial exams (2). It is worthy to mention that the individuals were asymptomatic. This collaborates to the statement of Oluboka et al. that is essential for physicians to clinically monitor for and inform patients about the signs and symptoms of reduced blood cell lineages (5). Moreover, both subjects had a full recovery in a month and this fact could suggest that pancytopenia secondary to VPA could be reversible on discontinuation of the drug (2).

In the Stewart et al. study, the VPA rechallenge using titrated doses was beneficial since the subject did not develop pancytopenia (2). In this way, in the present case, the 50% increase in the dose caused a decrease in red blood cells, white blood cells, and platelets. However, when the VPA dose was discontinued the laboratory tests returned to

**TABLE 2.** Case reports of VPA rechallenge after VPA-PCP

References		Stewart	Present case	
Age(y)/Sex		73/Male	38/Female	
Comorbidities		Bipolar disorder, coronary artery disease, diabetes mellitus, hypertension, osteoporosis, benign prostatic hypertrophy	Epilepsy, hypothyroidism	
Medications in use		VPA, sertraline, epoetin alfa, terazosin, finasteride, omeprazole, aspirin, and calcium with vitamin D	VPA, levothyroxine	
First time VPA	Indication	Bipolar disorder	Secondary epilepsy	
	Dose before PCP	500mg bid	500mg bid	
	Time of VPA use before pancytopenia	10y	3y	
	Evidence of PCP	Routine laboratorial exam without dose adjustment. The subject was asymptomatic.	Routine laboratorial exams due to dose adjust. VPA increased to 500mg tid. The subject was asymptomatic.	
	PCP	RBC	Erythrocytes $3.0 \times 10^6 / \text{mm}^3$	Hemoglobin 9,8mg/dL
		WBC (absolute neutrophil count)	2000	1600
		Platelets	58,000	83,000
	Management	VPA was discontinued. Lithium was started.	VPA was decreased to 500mg bid.	
	Time between management and normal laboratorial tests	7d	30d	
	Time between VPA-PCP and VPA-rechallenge	More than 0.5y	1y	
VPA rechallenge	Indication	Uncontrolled mood refractory to other drugs	New seizures onset	
	VPA dose and adjust	Started, and titrated to a maximum dosage of 1500 mg	500mg bid, adjusted to 500mg tid	
	Serum level (mg/L)	40-50	70	
	PCP	No	Yes	
	Management	Therapy maintained	VPA discontinued. Carbamazepine was started. After 60d, laboratory tests were within normal limits.	

Abbreviations: bid, twice a day; d, days; PCP, pancytopenia; RBC, red blood cells; tid, three times a day; VPA, valproic acid; WBC, white blood cells; y, years

normal limits. Therefore, this contributes to the hypothesis that VPA-pancytopenia probably is a dose-dependent side effect as well as the other hematological abnormalities such as thrombocytopenia (2,5).

The mechanism to explain pancytopenia secondary to VPA is probably based on bone marrow aplasia. The VPA possibly induces an immunological response, which increases circulating antibodies of immunoglobulin M (IgM) and turns Coombs test positive (6,7). This misleading response could cause bone marrow toxicity and pathologic findings such as hypocellularity with dyserythropoietic (5-7).

## CONCLUSIONS

Our report suggests the importance of routine blood monitoring tests in patients using VPA, especially when the dosage is adjusted. Moreover, it is probably preferable that VPA is substituted by another drug in the case of a hematologic side effect since its maintenance could be potentially harmful, although reversible. The pancytopenia is a life-threatening condition, and physicians should inform patients about the signs and symptoms of this adverse effect.

*Conflict of interest:* none declared  
*Financial support:* none declared

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