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Valproic Acid-Induced Thrombocytopenia-Related Spontaneous Systemic Bleeding

Authors' Contribution:

Study Design A
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Manuscript Preparation E
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Funds Collection G

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None declared

Patient: Female, 57-year-old
Final Diagnosis: Valproic-acid induced thrombocytopenia
Symptoms: Bleeding • bleeding • hemorrhage • vaginal bleeding
Medication: —
Clinical Procedure: —
Specialty: Neurology • Pharmacology and Pharmacy

Objective: Unusual clinical course

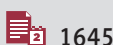
Background: Valproic acid is utilized for the management of various disease states, but coagulation changes, such as thrombocytopenia, can limit use. Valproic acid is a highly protein-bound drug. Serum levels of 50–100 mcg/mL are considered therapeutic, with minimal risk of toxicity when maintained within the recommended therapeutic index. We present a case of valproic acid-induced thrombocytopenia associated with spontaneous systemic bleeding.

Case Report: A 57-year-old woman with history of generalized anxiety disorder and choreiform movements presented to the Emergency Department with 1 day of oral and vaginal bleeding. The patient had been started on valproic acid for choreiform movements 3 weeks prior. On physical exam, the patient was noted to have atraumatic contusions and ecchymosis. A CT head revealed left temporal frontal subdural hematoma (4.5 mm), acute subdural hematoma along the posterior aspect of the interhemispheric falx (5 mm), mass effect on the right lateral ventricle, and an approximately 3 mm right-to-left midline shift. Laboratory testing was notable for platelets 4000/μL, hemoglobin 7.3 g/dL, hematocrit 23.1%, fibrinogen 467 mg/dL, and valproic acid random level 26.3 μg/mL. Thromboelastography revealed normal values except for a decreased maximum amplitude of 33.4 mm.

Conclusions: Although the clinical relevance is still debated, few case reports of significant bleeding related to valproic acid-induced thrombocytopenia exist. To the best of our knowledge, this is the first case report of spontaneous systemic bleeding due to valproic acid-induced thrombocytopenia in the setting of normal fibrinogen levels. Furthermore, this report demonstrates the potential risk of thrombocytopenia with subtherapeutic VPA levels.

MeSH Keywords: Bleeding Time • Thrombocytopenia • Valproic Acid

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Background

Valproic acid (VPA) is thrombocytopenia a highly protein-bound antiepileptic drug utilized for the management of a variety of disease states. Serum levels of 50–100 mcg/mL are considered therapeutic, with minimal risk of toxicity when maintained within the recommended therapeutic index. While benefits of therapy have been well described, valproic acid-induced coagulation changes can limit use. Thrombocytopenia occurs in approximately 12–18% of patients. While it is a recognized adverse drug reaction associated with use, it rarely requires therapy discontinuation. We present a case of valproic acid-induced thrombocytopenia associated with spontaneous systemic bleeding. This case highlights the importance of appropriate monitoring during use of valproic acid.

Case Report

A 57-year-old woman with a history of generalized anxiety disorder and choreiform movements presented to our Emergency Department with 1 day of oral and vaginal bleeding. The patient had a longer-term history of anxiety, with worsening in the last 8 months. The patient was diagnosed with chorea 46 days prior. According to her family, the choreiform movements were noted to have worsened over the past 3 days. Home medications included levetiracetam 750 mg by mouth twice daily and VPA 250 mg by mouth 3 times daily. The patient was on treatment day 21 of VPA for management of choreiform movements.

The patient was admitted 7 weeks before for a traumatic subacute right frontoparietal subdural hematoma without significant mass effect, with a hospital course complicated by methicillin-susceptible *Staphylococcus aureus* bacteremia. Her admission Glasgow Coma Scale (GCS) was 15, although she was noted to have choreiform type movements of her arms, legs, and trunk. The patient reported involuntary movements started 6 months prior, as well as a family history of abnormal movements, but was unable to provide more details. Neurology was consulted and ruled out a diagnosis of dystonia, as the patient denied antipsychotic or antidepressant use. Evaluation for movement disorders including movement disorder secondary to hereditary hemochromatosis, malignancy, vasculitis, Wilson's disease, atypical parkinsonism, Pantothenate kinase-associated neurodegeneration, and Huntington's, and all were determined to be negative. The patient was initiated on clonazepam 0.5 mg twice daily and levetiracetam 250 mg twice daily for chorea. Due to lack of patient response, increased dosing with levetiracetam 750 mg twice daily and clonazepam 0.5 mg 3 times daily was trialed. Valproic acid 250 mg 3 times daily was added on prior hospitalization day 22. Platelet count on prior admission was



Figure 1. CT head on admission. A CT head without contrast was ordered and revealed left temporal frontal subdural hematoma (4.5 mm), acute subdural hematoma along the posterior aspect of the interhemispheric falx (5 mm), mass effect on the right lateral ventricle, and an approximately 3-mm right-to-left midline shift.

139 000 μ L and 90 000 μ L at the time of VPA initiation. The patient was discharged with plans for genetic testing outpatient on hospital day 31 with a GCS of 15 and platelet count of 122 000 μ L. Discharge medications included clonazepam 0.5 mg by mouth twice daily, levetiracetam 750 mg by mouth twice daily, and VPA 250 mg by mouth 3 times daily.

On arrival, the patient's vital signs included a blood pressure of 131/91 mm Hg, heart rate of 120 beats/min, respiratory rate of 16 breaths/min, and temperature of 36.5°C. The patient had a GCS of 15 on admission. On physical exam, the patient was noted to have atraumatic contusions and ecchymosis throughout the chest, abdomen, back, upper and lower extremities, and left periorbital area. Current home medications included levetiracetam 750 mg by mouth twice daily and VPA 250 mg by mouth 3 times daily; clonazepam was not continued following prior discharge for unknown reasons. A CT head without contrast was ordered and revealed left temporal frontal subdural hematoma (4.5 mm), acute subdural hematoma along the posterior aspect of the interhemispheric falx (5 mm), mass effect on the right lateral ventricle and approximately 3 mm right-to-left midline shift (Figure 1). Despite combination pharmacotherapy, the patient was noted to have large-amplitude choreiform movements. She was admitted to an intensive care unit for further management.

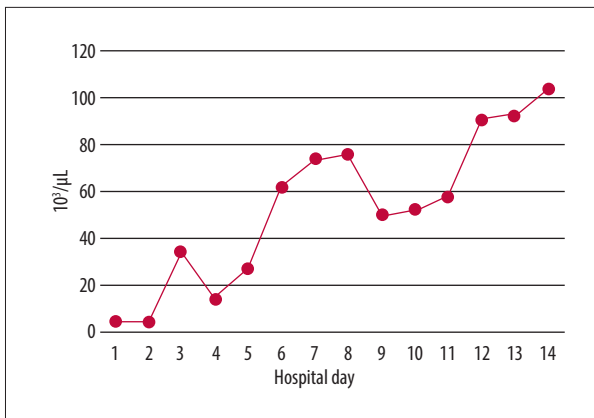


Figure 2. Platelet count. Measured serum platelet count ($10^3/\mu\text{L}$) from hospital days 0 to 14. The degree of thrombocytopenia was significant on day 0, and serum platelet counts remained below $50\,000/\mu\text{L}$ until hospital day 6. The serum platelet count normalized at above $100\,000/\mu\text{L}$ on hospital day 13 and until discharge.

Routine hematology testing revealed white blood cells $14.6 \times 10^6/\mu\text{L}$, red blood cells $2.75 \times 10^6/\mu\text{L}$, platelets $4000/\mu\text{L}$, hemoglobin 7.3 g/dL , hematocrit 23.1% , prothrombin time (PT) 15.7 secs , partial thromboplastin time (PTT) 30.4 s , and fibrinogen 467 mg/dL . Although the time of the last VPA dose was unclear, VPA level was $26.3\text{ }\mu\text{g/mL}$ (reference range: $50\text{--}100\text{ }\mu\text{g/mL}$). Valproic acid was held on admission in the setting of thrombocytopenia, with the trend in platelet count shown in Figure 2. Hematology data obtained 15 days prior at the time of hospital discharge was insignificant, with all values within normal limits. Except for a decreased maximum amplitude of 33.4 mm (reference range $52\text{--}71\text{ mm}$), thromboelastography (TEG) revealed normal values. Other causes of thrombocytopenia were evaluated, including disseminated intravascular coagulation and heparin-induced thrombocytopenia. Despite a positive heparin-platelet factor 4 (heparin-PF4)-related antibody, the serotonin release assay was negative. As the patient had not received heparin therapy in the prior admission, the heparin-PF4-related antibody was deemed a false-positive and the possibility for heparin-induced thrombocytopenia was eliminated. On hospital day 2, the VPA level decreased to $<10\text{ }\mu\text{g/mL}$. The fibrinogen level decreased slightly to 367 mg/dL , in addition to a significant decrease in hemoglobin to 5.3 g/dL . A repeat CT of the head on hospital day 2 showed stable size of the subdural hematomas with mild improvement in midline shift.

Hematology was consulted on hospital day 1 and the patient was initiated on methylprednisolone 60 mg intravenous 3 times daily. Following an acute decrease in platelet count on hospital day 4, intravenous immune globulin 1 g/kg was ordered. Due to the severity of thrombocytopenia and lack of response, VPA was

discontinued on admission and not re-initiated. Clonazepam was not re-initiated as it was no longer a current outpatient therapy. Levetiracetam was continued throughout hospital admission until discharge. Following discontinuation of VPA, platelet counts improved over the next 3 weeks. The patient was hospitalized for a total of 21 days, with a course complicated by altered mental status, urinary tract infection, *Escherichia coli* bacteremia, and sepsis. On hospital day 21, the patient was discharged with a platelet count of $108\,000$ and GCS of 14.

Discussion

Valproic acid is a branched short-chain fatty acid derived from valeric acid, a naturally occurring substance [1]. Valproic acid is used in the management of a variety of seizure and psychiatric disorders [2]. While its mechanism is complex, it is most known for its effects on γ amino butyric acid (GABA) levels in the brain. Valproic acid therefore inhibits the degradation of GABA, increasing concentrations of the inhibitory neurotransmitter. Furthermore, VPA blocks voltage-gated ion channels, including sodium, potassium, and calcium. Inhibition of these ion channels results in the reduction of neuronal firing frequency.

Valproic acid is a highly protein-bound drug, with $87\text{--}95\%$ bound to serum protein [3]. High protein binding is associated with low drug clearance; therefore, monitoring of serum levels is crucial. Serum levels of $50\text{--}100\text{ mcg/mL}$ are considered therapeutic, with significant toxicity when levels exceed 100 mcg/mL . If feasible, free levels can also be obtained, and a reference range of $5\text{--}15\text{ mcg/mL}$ is considered therapeutic [4]. Our patient had mildly decreased albumin levels at the time of drug initiation (3.7 mg/dL), and at the time of presentation with hemorrhage (3.3 mg/dL). The risk of toxicity associated with therapy can be minimal if serum levels are maintained within the recommended therapeutic index. Despite appropriate monitoring, toxicity can occur. Valproic acid levels were 26.3 mcg/mL and $<10\text{ mcg/mL}$ on hospital days 1 and 2, respectively.

Black box warnings for hepatotoxicity, teratogenicity, pancreatitis, and acute liver failure and mortality in patients with mitochondrial disease are notable. While careful monitoring is recommended in those with renal dysfunction, use is not recommended in mild-to-moderate hepatic dysfunction and is contraindicated in severe hepatic dysfunction. Our patient had no baseline hepatic dysfunction or contraindications to use prior to initiation.

Many studies have reported hematologic abnormalities associated with VPA, such as thrombocytopenia, inhibition of platelet aggregation, and bleeding. Thrombocytopenia occurs in approximately $12\text{--}18\%$ of patients [3]. Although the

clinical relevance is still debated, few case reports of significant bleeding related to VPA-induced thrombocytopenia exist. In general, the adverse effects associated with the hematologic abnormalities are mild at presentation (bruising, petechia, hematoma, and epistaxis) or identified in laboratory assays. Platelet counts may also normalize with continued treatment. Current recommendations include dose reduction or drug discontinuation if hemorrhage, significant bruising, or coagulation abnormalities develop. Weekly complete blood counts should be monitored until return of normal platelet counts [5]. Due to the risk of thrombocytopenia, platelet counts should be obtained prior to initiation and periodically during therapy. Our patient developed significant thrombocytopenia despite subtherapeutic levels on hospital days 1 and 2. While we were unable to confirm the exact time from last dose prior to drawing of the serum level, we were able to confirm that the dose was administered within 24 h prior to admission. The probability of thrombocytopenia increases with total valproate levels ≥ 110 mcg/mL in females or ≥ 135 mcg/mL in males [6]. Our patient did not meet these thresholds for increased risk, with a level of 26.3 mcg/mL, thus demonstrating a potential risk of thrombocytopenia in the setting of subtherapeutic VPA levels.

In addition to thrombocytopenia and decreased platelet function, hemostatic abnormalities include decreased fibrinogen, and von Willebrand factor levels. Previous reports of systemic bleeding and intracranial hemorrhage associated with use were in the setting of decreased fibrinogen levels [7]. Our patient had normal fibrinogen levels of 467 mg/dL and 367 mg/dL on hospital days 1 and 2, respectively. Thromboelastography on hospital day 1 further confirmed the absence of coagulation abnormalities.

Conclusions

The absence of other causes of thrombocytopenia and the temporal relationship to the initiation of valproic acid, support the diagnosis of VPA-induced thrombocytopenia. Severe thrombocytopenia in our patient resulted in the formation of multiple subdural hematomas, as well as vaginal and oral bleeding. To the best of our knowledge, this is the first case report of spontaneous systemic bleeding due to valproic acid-induced thrombocytopenia in the setting of normal fibrinogen levels [8]. Furthermore, this report demonstrates the potential risk of thrombocytopenia with subtherapeutic VPA levels.

Conflicts of interest

None.

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