Repeated Adverse Hematologic Reactions Associated With Valproic Acid Use in a Patient With Acquired Renal Insufficiency

To the Editor: The oral loading of valproic acid (VPA) is mostly safe and leads to more rapid anti-manic effects than standard titration of offending drugs.[1] Although hematologic toxicities such as thrombocytopenia, neutropenia, and even pancytopenia associated with VPA have been reported, as far as we know, serial acute adverse effects like pancytopenia resulting from oral loading of VPA have rarely been reported.[2] We present here a case of repeated hematologic adverse effects associated with VPA treatment in a patient with acquired renal insufficiency.

Case Report

"Ms. L" was a 50-year-old woman with a 28-year history of bipolar I disorder, who had been taking a stable regimen of 600 mg/day lithium and 1,000 mg/day VPA without any adverse hematologic effects over the past 5 years. She accidentally suffered from lithium intoxication in May of 2008 and was diagnosed with lithium-related chronic renal insufficiency (serum creatine level: 2.8 mg/dL). The clinician discontinued lithium and prescribed 1,400 mg/day VPA as maintenance therapy for her bipolar disorder. Three months later, thrombocytopenia was noticed during the laboratory follow-up examination, and VPA was switched to 400 mg/day of carbamazepine. The patient recovered from thrombocytopenia within 1 week after the cessation of VPA. One month later, she was admitted to our psychiatric inpatient unit because of worsened manic symptoms. On admission, her renal function was abnormal (serum creatine level: 2.8 mg/dL), and, thus, 1,000 mg/day VPA was reintroduced, and the platelet count was monitored. Risperidone (2 mg/day) was concurrently administered. Five days after restarting the VPA treatment, a trend of pancytopenia was detected during a routine laboratory testing. The patient was found to have a white blood cell count of 4,200 cells/mm^3, a red blood cell count of $2.24\times106/\mu L$, hemoglobin level of 7.4 g/dL, a platelet count of $177\times103/\mu L$, 41.7% neutrophils, and a VPA level of 79 μg/mL (normal range: 50–100 μg/mL). There was no fever or bleeding tendency. VPA therapy was discontinued, 8 days after which, the pancytopenia resolved spontaneously without any complication, despite the concurrent use of trileptal and risperidone to control her mood symptoms.

Discussion

The repeated hematological changes experienced by this patient are considered to be drug-related because of the cause-and-effect relationship between the administration of the drug and their appearance, and their recurrence with re-challenge. Moreover, the Naranjo Adverse Drug Reaction Probability Scale [3] score for this case indicated that VPA is a probable causative factor of hematological adverse reactions.

Although hematologic toxicities associated with VPA, varying in onset and severity, are common, they usually occur in the presence of some possible risk factors, such as serum VPA level greater than 100 μg/mL, old age (>65 years), VPA dosage greater than 1,000 mg/day, and duration of exposure.[4–6] Our patient developed pancytopenia upon re-challenge with 1,000 mg/day VPA, which was within the allowed therapeutic limit. Moreover, adjunctive risperidone treatment had no influence on the steady-state pharmacokinetics of valproic acid, suggesting that this combination was safe and well tolerated.[7] This led us believe that our patient might have other underlying risk factors in addition to a longer duration of exposure and higher dose of VPA.

Previous reports suggested that hematologic toxicity could be the result of an elevated concentration of free VPA.[8,9] As we know, VPA is highly bound to plasma proteins.[10] Furthermore, uremic compounds could displace VPA from protein-binding,[11] and hemodialysis, which increases the amount of free fatty acid that displaces VPA, and would ultimately lead to increased free-VPA level.[12] According to the report of U.S. Food and Drug Administration, a 27% reduction in the clearance of unbound valproate is seen in patients with renal impairment (Cl_{cr} <10 mL/min). Taken together, these findings modestly suggest that chronic kidney disease by itself or confined to those with end-stage renal disease (ESRD) seems to predispose patients to the development of serious hematologic complications. Although we did not determine the free VPA level in our patient because of limited resources, this might be a more plausible hypothesis at present.

Our case spotlights the fact that VPA-related hematologic toxicity can occur even when the VPA

plasma levels are within the therapeutic limit. When a patient's pathophysiological conditions change, clinicians should be cautious about the possibility of increased free VPA level. Further study is needed to examine whether renal insufficiency (or ESRD) is a predisposing factor for VPA-induced hematological toxicity, even within normal therapeutic levels.

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