Case Report

Hyperammonemic Encephalopathy due to Valproic Acid and Topiramate Interaction

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Abstract
Valproic acid-induced hyperammonemic encephalopathy is a rare yet serious adverse drug reaction. Medication interactions such as valproic acid and topiramate can precipitate an event. We present the case of a 52-year-old female that presented with acute mental status change and hypersomnolence due to hyperammonemia caused by a valproic acid derivative. The patient improved after withdrawal of the offending medications and treatment with lactulose. Clinicians should remain hypervigilant in monitoring for valproic acid-induced hyperammonemic encephalopathy and risk factors such as polypharmacy.

1. Introduction
Valproic acid (VPA) is considered one of the first line treatment agents for psychiatric conditions such as bipolar disorder [1]. Despite the widespread use of this medication in psychiatric disorders, little literature has been published reviewing the association with VPA and hyperammonemic encephalopathy in psychiatric patients. Although common in the neurology literature, the first report of hyperammonemic encephalopathy associated with VPA use in psychiatric patients was in 1995 by Settle Jr. [2]. In 2012, a review by Chopra et al. reported that only 30 cases of valproate-induced hyperammonemic encephalopathy (VHE) along with 5 cases from their institution (total 35 cases) had been discussed in the literature [3]. Even though the development of VHE seems rare in this patient population, the literature addressing the presenting symptoms, risk factors, and treatment for VHE has been well documented.

Along with potential electroencephalography (EEG) findings, VHE is commonly characterized by lethargy, vomiting, cognitive slowing, focal neurological deficits, and decreasing levels of consciousness ranging from drowsiness to coma in patients on VPA treatment [3, 4]. Among the prevailing risk factors for this condition, the most widely accepted are urea cycle disorders, carnitine deficiency, and polypharmacy [5–8]. Common medications that may contribute to the development of VHE when used concurrently are phenytoin, phenobarbital, and topiramate.

2. Case
A 52-year-old female was brought from a care home to the hospital for altered mental status. Patient was nonverbal on arrival to hospital; therefore, history of events was given by case manager. Four days prior to admission she visited her psychiatrist where her medications were adjusted. According to the case manager from the care home, the patient was started on clonazepam 1 mg daily. Divalproex sodium 500 mg twice daily was restarted and quetiapine was increased from 100 mg to 150 mg in the evening. Following these adjustments, the patient was noted to have increased somnolence. Her past medical history included schizoaffective disorder, essential tremor, migraines, seizure disorder, cerebrovascular accident, and chronic obstructive pulmonary disease. Home medications were as follows: primidone 200 mg twice daily,
Hypermunmonemia is a known side effect of administration of VPA and its derivatives. Raja and Azzoni assessed adult patients admitted to a psychiatric unit receiving a mood stabilizer such as VPA and found that 51.2% of patients receiving VPA had asymptomatic hyperammonemia [9]. While the prevalence of asymptomatic hyperammonemia in this study is high, it is important to note that VHE is rare and often hard to distinguish from the development of acute psychosis. Per package labeling recommendations, there is no evidence for routine screening of ammonia levels in patients receiving VPA [10]. However, if a patient presents with unexplained lethargy and vomiting or changes in mental status then an ammonia level should be measured. Symptoms may vary from mild to severe changes in cognitive and behavioral function including acute mental status change, lethargy, cognitive slowing, increased seizure frequency, and death [2, 11, 12]. The diagnosis of VHE can be established by ruling out other causes of impaired consciousness along with laboratory (VPA level, ammonia level) and diagnostic studies (EEG). However, the notion that there is a correlation between symptoms and VPA daily dose or serum concentrations has been somewhat controversial. Upon review of previously published reports, there appears to be no discernible relationship between development of VHE and daily doses nor serum VPA levels [3, 4, 11, 13].

In VHE, the main pathophysiological mechanism involves the inhibition of an enzyme involved in the urea cycle with subsequent development of hyperammonemia [4]. Ensuing CNS toxicity due to the hyperammonemia is thought to be mediated by excessive activation of the NMDA type of glutamate receptors [14]. This sequence of events leads to the development of VHE. Urea cycle disorders, carnitine deficiency, and polypharmacy provide a framework for the above mechanisms to occur more readily. Previous studies have shown that topiramate inhibits both urea cycle and glutamate synthetase activity which are two of the primary mechanisms involved in the development of VHE [8, 15]. The polypharmacy our patient experienced (received both topiramate and divalproex sodium) was thought to be the cause of her acute mental status change. While there is no consensus regarding treatment other than withdrawing VPA therapy, several approaches have been used successfully in clinical practice [3]. These include supplementation with carnitine, lactulose, or neomycin and protein restriction [3]. For asymptomatic elevations in ammonia levels that persist, package labeling recommends to consider discontinuation of the medication [10].

4. Conclusion

We present the case of a 52-year-old female that developed presumed VHE after the addition of VPA to her home medication of topiramate. Given her high normal VPA level, elevated ammonia, presenting symptoms, and EEG findings, the diagnosis of VHE was made. This can be further substantiated by the Naranjo probability scale for adverse drug reactions (ADR) [16]. The score for this patient is a 6 which places her in the probable ADR category. This case highlights the need for clinician awareness regarding medication interactions and potential adverse effects. While VPA is commonly used in neurology and psychiatric patient populations, clinicians treating psychiatric patients may not be as familiar with all of the interacting antiepileptic medications. Since VHE if often hard to distinguish from acute psychosis, it is important to...
consider all aspects of the patient case including medication interactions.

**Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**


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