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Editor-in-Chief
Wayne J. Katon MD
University of Washington Medical School, Dept. of Psychiatry, Seattle, WA, USA

"The Real Mechanism of VPA-induced Hyperammonemia Remains Unknown"

Dear Wayne J. Katon:

We appreciate the two reviewers' constructive and valuable comments, which have helped us to amend the manuscript. Some important amendments to the text are as the following contents. We hope that you will take this into consideration.

Thank you.
Sincerely yours

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Oct, 2010

Answers to Reviewer #1

General comments

Comment 1: The normal range in your VPA-treated patients may be carnitine depleted despite having normal carnitine serum levels

Answer: We agree with the reviewer #1's point that the normal carnitine measured in VPA-treated patient may not be relevant while carnitine is mostly stored in the muscles (Shapiro and Gutman, 1991). Reviewing from the literature, hypocarnitinaemia has not been confirmed in VPA-treated patients, suggesting that the carnitine checking is not justified. (Borum and Bennett, 1986 ;Coulter DL, 1991).

Concerning our case, the normal carnitine serum level couldn't be excluded out carnitine-deficient state. We added a sentence to illustrate such limitation on ***Page 5 (line 9~10)***.

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*Title Page

The Real Mechanism of VPA-induced Hyperammonemia Remains Unknown

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Both authors Hung and Li contributed equally to this work

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Key Words: Valproic acid; Hyperammonemia; Risk factors, Early recognition

The Real Mechanism of VPA-induced Hyperammonemia Remains Unknown

Abstract

Valproic acid (VPA) is a well-tolerated and effective agent for the treatment of epilepsy, bipolar disorder, and schizoaffective disorder. Several case reports have indicated that VPA may induce serious symptomatic hyperammonemia. Based on analysis of susceptible patients, several possible mechanisms and risk factors have been proposed to identify the patients at risk. Nevertheless, we report the case of a schizoaffective patient who developed severe hyperammonemia occurring after brief exposure to VPA, despite the absence of any known risk factors. Until now, early recognition of the signs and symptoms of hyperammonemia is crucial to managing this unusual adverse reaction.

1. Introduction

Valproic acid (VPA) is an effective antiepileptic agent that shows efficacy in the treatment of bipolar and schizoaffective disorders. In addition to its particular set of adverse reactions, asymptomatic hyperammonemia in the absence of abnormal liver function secondary to VPA is common even with therapeutic serum levels [1]. However, recent publications have documented several cases of VPA-associated serious symptomatic hyperammonemia. Several risk factors were supposed for it [1, 2]. We describe a case of

serious symptomatic hyperammonemia associated with VPA administered as monotherapy in the absence of any known predisposing factors or physical comorbidities.

2. Case report

A 21-year-old woman was admitted because of acute exacerbation of hallucinations and aggressive behavior toward her family. After being diagnosed 3 years previously, she was treated with risperidone, 2 mg/day. However, after 1 year of regular treatment, she discontinued the medication because of the side effect of amenorrhea. For the 2 years prior to the current hospitalization, she had experienced residual auditory hallucinations

The exacerbation of the patient's psychotic symptoms 1 week prior to admission resulted in poor nutritional intake. Laboratory testing revealed fasting blood glucose 55 mg/dL. Complete blood cell count (CBC) with differential count (DC), liver, kidney, thyroid function, and serum electrolytes were normal.

The patient was intially prescribed amisulpride, 100 mg/day, titrated up to 600 mg/day in 2 weeks. At the end of the 2 weeks, she had fair oral nutritional intake with daily protein consumption 50g and fasting blood glucose 118 mg/dL. Nevertheless, not only did psychotic symptoms persist, but also gradual onset of manic symptoms was noted, including elated mood, talkativeness, increased goal-directed activity, and flight of ideas. Amisulpride was discontinued and VPA, 500 mg/day, was begun as monotherapy, titrated up to 750 mg/day

within 4 days. However, this was followed by the sudden development of nausea, vomiting, drowsiness, disorientation, and ataxia, with a Glasgow coma scale E2V3M4. Biochemistry examinations showed VPA level 107.7 μg/mL and elevated ammonia 228 μg/dL. Brain electroencephalography at that time showed intermittent slow waves in both hemispheres. CBC/DC didn't reveal leukocytosis or coagulopathy. Urinalysis, serum electrolytes, blood glucose, kidney, liver function, abdominal sonography, and brain computed tomography were all normal.

VPA was discontinued, and intravascular fluid supplementation and lactulose were provided. Within 2 days, the ammonia was reduced to 24 μg/dL, and the patient demonstrated improved consciousness, fair orientation, and stable gait. She was then administered aripiprazole, 5 mg/day, with titration up to 10 mg/day within 1 week. Clonazepam, 3 mg/day, was added as adjuvant therapy. Follow-up for 3 months revealed ammonia and liver function test results within the normal ranges.

We performed serum amino acid analysis, which showed a normal carnitine level of 35 mmol/L and a normal glutamine level. Genetic study of all 10 exons (including the exon–intron boundaries) of the uric cycle enzyme OTC (ornithine transcarbamylase) revealed no specific findings, with the same sequence of primers as normal controls as described by Huang et al. [3].

3. Discussion

Hyperammonemia is a common problem for the patients receiving VPA treatment. For the majority of patients, the VPA-induced hyperammonemia (VIH) is asymptomatic. Nevertheless, some cases of serious symptomatic VIH at both therapeutic and supratherapeutic concentration of VPA, have also been reported [1, 2].

The progression and severity of hyperammonemia are widely variable with each patient. And, through assessment of those symptomatic patients, several possible risk factors and mechanisms for development of symptomatic hyperammonemia have been proposed, including urea cycle enzyme deficiency, polypharmacy, complicated medical condition, mental retardation, dietary restrictions such as a vegetarian diet, carnitine deficiency due to genetic abnormalities, and infancy [1, 2, 4]. These analyses can provide clinicians to investigate the pathophysiology of VIH as well as for prediction of the severe adverse reaction.

In fact, the patients who developed symptomatic VIH have at least one of these risk factors in the earlier report. For example, in the Dealberto's review of VHE, polypharmacy was observed for all 14 patients with an average of 3.7 drugs [2]. Additionally, despite "unknown" risk factor was listed for four of total 14 cases in the Carr and Shrewsbury's review about symptomatic hyperammonemia due to VPA, all the four patients received polypharmacy, 2 of them were alcohol/benzodiapine dependence, one was mental retardation,

and one had diabetic ketoacidosis [1]. Furthermore, only the patient reported by Nicolai et al. [5] was tested for plasma carnitine concentration and the two patients reported by Shan et al. [6] were tested the mutation of the ornithine transcarbamoylase gene. Our patient received VPA monotherapy and the test for abnormal carnitine and mutation of OTC gene were negative. The patient didn’t have complicated medical condition, mental retardation, and was not vegetarian. In fact, most patients who have any of these specific risk factors that have been proposed do not get VIH [7, 8, 9].

Despite several potential risk factors for the current case are excluded, some limitations require considered. First, since the carnitine is mostly stored in muscles, the normal serum carnitine in our case couldn't be excluded out carnitine-deficient state [10]. Additionally, despite OTC deficiency is the most common urea cycle disorder and the one most frequently associated with VIH [3]. We didn’t screen other enzymes of the uric cycle which may be involved in VIH.

Our case highlights that the real mechanism of VIH remains unknown. Clinician must keep in mind that early recognition of the signs and symptoms is crucial to managing this unusual adverse reaction.

Reference

[1] Carr RB, Shrewsbury K. Hyperammonemia due to valproic acid in the psychiatric setting. Am J Psychiatry 2007;164:1020–7.

[2] Dealberto MJ. Valproate-induced hyperammonaemic encephalopathy: review of 14 cases in the psychiatric setting. Int Clin Psychopharmacol 2007;22:330–7.

[3] Huang YT, Chien Y, Yeh HY, Lin SJ, Lu FL, Chou SP, Lin JM, Chiang SC, Hwu WL. Phenotype and genotype analyses of ornithine transcarbamylase deficiency in Taiwanese. J Formos Med Assoc 2003;102:851–6.

[4] Raskind JY, El-Chaar GM. The role of carnitine supplementation during valproic acid therapy. Ann Pharmacother 2000;34:630–8.

[5] Nicolai J, Smith SJ, Keunen RW. Simultaneous side effects of both clozapine and valproate. Intensive Care Med 2001;27:943.

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[7] Hamed SA, Abdella MM. The risk of asymptomatic hyperammonemia in children with idiopathic epilepsy treated with valproate: relationship to blood carnitine status. Epilepsy Res. 2009;86:32-41.

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[10] Shapiro YG, Gutman A. Muscle carnitine deficiency in patients using valproic acid. J Pediatr. 1991;118:646-9.

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