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Differential ammonia decay kinetics indicates more than one concurrent etiological mechanism for symptomatic hyperammonemia caused by valproate overdose

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Abstract

Valproic acid (VPA) has successfully been used in the therapy of a number of conditions including absence seizures, partial seizures, tonic-clonic seizures, bipolar disorder, schizoaffective disorder, social phobias, neuropathic pain and migraine headaches. There is a high rise in number of cases of toxicity due to overdose of VPA. Hyperammonemia, a common side-effect of VPA, is caused by several proposed etiologies, reported as having uncertain correlation with VPA dose or concentration. We present here a case of a 25-year-old female patient with a past history of psychiatric complaints, presented with elevated serum VPA levels associated with elevated venous ammonia levels subsequent to VPA overdose. Later in the presence of sub-therapeutic serum VPA levels her venous ammonia levels remained raised and slowly down-trending. VPA levels and ammonia levels were found to be normal after 14 days. Patient was treated with levocarnitine. Her liver enzymes were never elevated. Different decay kinetics of venous ammonia in presence of high and low concentrations of VPA indicates that VPA can cause symptomatic hyperammonemia via more than one concurrent etiological mechanism. In this patient, the mechanisms causing hyperammonia secondary to VPA use were not related to hepatic damage or carnitine deficiency.

KEY WORDS: Ammonia, etiology of hyperammonemia, levocarnitine, valproic acid

Introduction

The success of valproic acid (VPA, 2-propylpentanoic acid), a short branched chain fatty acid, for the therapy of absence seizures, partial seizures, tonic-clonic seizures, bipolar disorder, schizoaffective disorder, social phobias, neuropathic pain and for the prophylaxis and treatment of migraine headaches has spurred investigation for its use in the treatment of other conditions.[1] Hyperammonemia (venous serum ammonia levels >35 μmol/L[2]) is a common side-effect of VPA use. Treatments for encephalopathy secondary to hyperammonemia as a side-effect of VPA treatment remain empirical and restoration of possible hepatic carnitine deficiency remains controversial.[3] While some authors have found a positive correlation between plasma ammonia level and VPA dose or concentration[4] others have found none.[5] We report a case of a patient with a past history of psychiatric complaints. Her elevated VPA levels were

associated with elevated ammonia levels as expected of a positive correlation. In contrast, later on in the patient's clinical course her raised venous ammonia levels were found to be slowly down-trending in the presence of sub-therapeutic serum VPA.

Case Report

The present case report is about a 25-year-old Hispanic female with a history of depression since age of 12 years, bipolar disorder, borderline personality disorder, purging type bulimia and history of suicide attempts at age 12 was admitted to the intensive care unit after attempted suicide by consuming an unknown number of VPA pills. This patient had recently started taking VPA (Depakote®) as a mood stabilizer at a dose of 250 mg at bed time about 3 days earlier, after a failed therapy. VPA was started 4 days after she discontinued topiramate. Patient was taking paroxetine 20 mg for depression; this was incremented to 40 mg at the time VPA was started. She reported that the change to VPA made her listless, “lowered” her mood, decreased her motivation, worsened her depression and caused suicidal thoughts. She overdoses herself on VPA which she took with alcohol. After ingesting the pills she notified her family who then brought her to the emergency room. On admission, her vitals were stable (blood pressure: 118/72 mm Hg; temperature: 98.7°F; pulse: 82 beats/min; oxygen saturation: 99% on room air). On initial examination she looked disheveled, although drowsy, was oriented to person, place and time. No focal neurological deficits, abnormal cardiologic or respiratory signs were found. Her abdomen was soft, non-distended and non-tender. Her electrocardiogram showed normal sinus rhythm. The complete blood count and comprehensive metabolic panel that was recorded initially and subsequently were unremarkable [Table 1]. The initial VPA and ammonia levels were elevated [Figure 1a]. Patient was administered activated charcoal and one dose of haloperidol 5 mg intramuscularly. Subsequently, she was administered oral lactulose once and then 1400 mg of levocarnitine orally every 6 h for the next 2 days. Her VPA levels which peaked after admission continued to trend down over the next 4 days, the ammonia levels also peaked subsequent to admission then showed an initial dip followed by a very slow down-trend [Figure 1a]. The normalized log-linear plot of VPA serum concentration over time showed a down-trending linear first-order kinetics with a calculated $t_{½}$ =15.08 h [Figure 1b] (expected $t_{½}$ for Depakote®: 9-16 h following oral dosing regimens of 250-1000 mg.[6] The serum ammonia normalized log-linear plot in contrast showed two different decay kinetics: initial sharp down-trend for VPA levels greater than 90.9 μg/mL but much slower downtrend for VPA levels less than 90.9 μg/mL down into the subtherapeutic range of 8.5 μg/mL. Patient continued to complain of lethargy for the next 4 days which subsequently alleviated. At 14 days the patient was asymptomatic and her ammonia levels found to be normal (<35 μmol/L).

Discussion

Recognition of symptoms of hyperammonemia remains a challenge especially in psychiatric patients. In a review of 11 case reports of symptomatic hyperammonemia in a psychiatric setting[3] it was noted that acute hyperammonemic encephalopathy in psychiatric patients may present in various ways, sometimes with subtle clinical features. The previously reported spectrum of clinical features included: improvement in mood, worsening of psychiatric symptoms, mild complaints of fatigue and delirium.[3] In our patient, hyperammonemia secondary to VPA overdose caused listlessness, “lowering” of mood, decreased motivation, worsening depression and suicidal ideation.

We observed presence of VPA in serum caused increased venous ammonia levels, which eventually trended down to normal after its cessation. Increasing VPA levels in serum was associated with increasing venous ammonia levels initially [Figure 1]. The peak concentration of ammonia noted was likely a decrement from the real peak based on the time to peak of Depakote® tablets being 4 h[6] (the patients initial VPA levels were measured at 2 h after she allegedly consumed the VPA while the next blood draw was 9 h later). We also made the following observations: (1) Raised venous ammonia levels may remain symptomatic for a significant period of time beyond discontinuation of VPA. (2) Existence of more than

one concurrent mechanism with different decay kinetics in the metabolism of ammonia in presence of high or low concentrations of serum VPA. Unmasking of an inherent urea cycle metabolic disorder could have amplified the differential decay rates of venous ammonia.

The possibility of more than one mechanism causing hyperammonia secondary to VPA use is suggested by the different proposed mechanisms of VPA metabolites causing hyperammonemia,[7] these include: (1) Propionic acid inhibiting the urea cycle enzyme carbamoyl phosphate synthetase I; (2) Valproyl-CoA or a closely related compound as a proximate inhibitor of mitochondrial ureagenesis; (3) Valproyl-carnitine ester causing a relative carnitine deficiency and (4) 2,4-dien-VPA inhibiting b-oxidation. Although, we cannot speculate on the mechanisms responsible for the different kinetics of decay of ammonia levels in the presence of down-trending VPA levels we can confidently state that non-elevated hepatic enzymes and hyperammonemia despite carnitine replacement indicated that hepatic damage and carnitine deficiency[8] had very little role in causing the slowly down-trending elevated ammonia levels in the presence of subtherapeutic serum VPA levels.

Hyperammonemia and psychiatric disturbance secondary to valproate use in our case showed a score of 9 by a Naranjo algorithm, indicating strong causality with the drug and placing it in causality category of "definite."[9] Our assessment of a high adverse reaction probability scale was based on the fact that there are previous conclusive reports of hyperammonemia secondary to VPA use with similar psychiatric features as presented in this case report, hyperammonemia occurred only after VPA use and eventually trended down to normal levels with discontinuation of VPA, patients psychiatric disturbance correlated with hyperammonemia, the patient symptomatically improved with drug discontinuation, there are no alternative explanation of hyperammonemia and altered mood in this case, the serum levels of VPA were elevated with concentrations known to be toxic and that toxic effects observed were more severe with high dose and less severe when secondary hyperammonemia decreased. This case report suggests that hyperammonemia, which is known to occur in about 50% patients treated with VPA, may have more than one concurrent etiologic mechanism with different decay kinetics which are not related to hepatic damage or carnitine deficiency.

Footnotes

Source of Support: Nil

Conflict Interest: No

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Figures and Tables

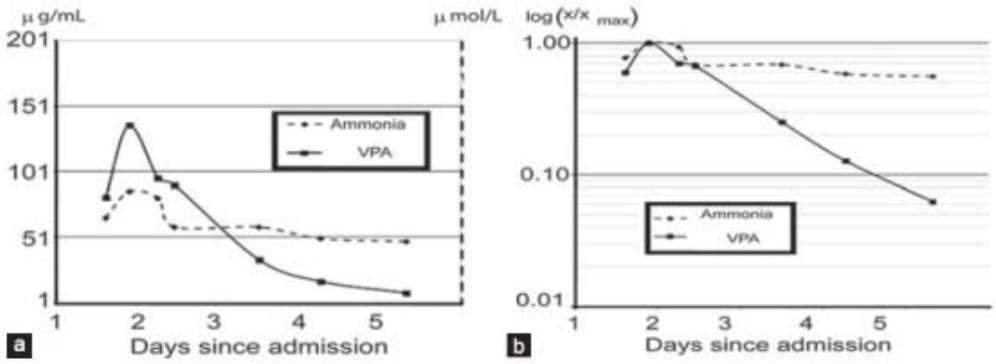
Table 1

CMP	
Sodium	143 (mmol/L)
Potassium	4.1 (mmol/L)
Chloride	107 (mmol/L)
Bicarbonate	26 (mmol/L)
Glucose	69 (mg/dL)
Urea nitrogen	10 (mg/dL)
Creatinine	0.5 (mg/dL)
Calcium	8.5 (mg/dL)
ALT	24 (U/L)
AST	14 (U/L)
Total bilirubin	0.3 (mg/dL)
Ethanol level	27 (mg/dL)
CBC	
WBC	7.4 (K/mm3)
RBC	4.34 (M/mm3)
Hemoglobin	13.2 (g/dL)
Hematocrit	39.1 (%)
Platelet	310 (K/mm3)

WBC = White blood cells, RBC = Red blood cell, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, CMP = Comprehensive metabolic panel, CBC = Complete blood count

Laboratory values of the patient at the time of admission

Figure 1



(a) Valproic acid (VPA) and ammonia levels as a function of time (days). Vertical axes: Straight line (left): VPA levels; dashed line (right): Venous ammonia levels. Day 1 indicates the day in which the patient overdosed herself. (b) Logarithm of normalized VPA and ammonia levels as a function of time in days. The normalization for each compound, for levels at each recorded time point (x) was to its recorded maximum level (xmax). The normalized log-linear plot of VPA showed linear first-order decay kinetics with a calculated t½ = 15.08 h (R^2 = 0.994)