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Case Report

Valproic Acid and Topiramate Induced Hyperammonemic Encephalopathy in a Patient With Normal Serum Carnitine

Martha G. Blackford, PharmD,[1,4] Stephanie T. Do, DO,[2] Thomas C. Enlow, MD,[3,4] and Michael D. Reed, PharmD[1,4]

[1]Divisions of Clinical Pharmacology and Toxicology and Rebecca D. Considine Research Institute, and [2]Pediatric Residency Program and [3]Neurodevelopmental Science Center, Akron Children's Hospital, Akron, Ohio, [4]Northeast Ohio Medical University, Rootstown, Ohio

A 17-year-old female developed hyperammonemic encephalopathy 2 weeks after valproic acid (VPA), 500 mg twice a day, was added to her regimen of topiramate (TPM), 200 mg twice a day. She presented to the emergency department (ED) with altered mental status, hypotension, bradycardia, and lethargy. Laboratory analysis showed mild non-anion gap hyperchloremic acidosis, serum VPA concentration of 86 mg/L, and urine drug screen result that was positive for marijuana. She was admitted to the pediatric intensive care unit for persistent symptoms, prolonged QTc, and medical history. Blood ammonia concentrations were obtained because of her persistent altered mental status, initially 94 µmol/L and a peak of 252 µmol/L. A serum carnitine profile was obtained at the time of hyperammonemia and was found to be normal (results were available postdischarge). VPA and TPM were discontinued on day 1 and day 2, respectively, as the patient's blood ammonia concentration remained elevated. On day 3, her mental status had returned to baseline, and blood ammonia concentrations trended downward; by day 4 her blood ammonia concentration was 23 µmol/L. VPA has been associated with numerous side effects including hyperammonemia and encephalopathy. Recently, drug interactions with TPM and VPA have been reported; however, serum carnitine concentrations have not been available. We discuss the possible mechanisms that VPA and TPM may affect serum ammonia and carnitine concentrations and the use of levocarnitine for patients or treating toxicity.

INDEX TERMS: hyperammonemia, levocarnitine, serum carnitine, topiramate, valproic acid

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INTRODUCTION

Valproic acid (VPA), a simple branched chain carboxylic acid, is effective for the treatment of a number of types of seizures, including tonic-clonic, myoclonic, absence and partial seizures. Multiple drug-drug interactions and drug-induced adverse effects have been associated with VPA use including numerous publications describing VPA-associated hyperammonemia, with or without hepatotoxicity.[1–5] More recently, case reports have described VPA-associated hyperammonemic encephalopathy in patients receiving the combination of VPA and topiramate (TPM), even in patients previously stable on different VPA regimens (Table).[6–12] The possible mechanism(s) for this drug-associated/ drug-induced toxicity when administered alone or in combination with other drugs is unknown, but many authors have speculated about the role of carnitine deficiency. We report the case of an adolescent female who developed hyperammonemic encephalopathy with a normal serum carnitine concentration after VPA was added to chronic TPM therapy.

CASE REPORT

The patient was a 17-year-old female with a history of juvenile myoclonic epilepsy (JME), currently receiving TPM and VPA (her only home medications) therapy, who was admitted to the pediatric intensive care unit (PICU) with altered mental status. Her condition had been diagnosed as seizure activity approximately 1 year prior to presentation, and she was started on TPM, 200 mg twice daily. Levetiracetam was added for breakthrough seizures; however, she failed to

Table. Reported Cases of Valproic Acid- and Topiramate-Associated Hyperammonemic Encephalopathy

Study ref.	No. of Patient Cases	Patient Age	AEDs	Symptoms	NH_4 Serum Concentrations	VPA Serum Concentrations	Drug Regimen Changes	Outcome
Hamer et al[6]	2	32 yo M	PB 200 mg/day, TPM 600 mg/day, VPA 1500 mg/day	Drowsy, nausea, slurred speech, somnolent, ataxia, horizontal nystagmus, abnormal EEG, ↑GGT	116 µmol/L, 2 days after ↑VPA (symptoms started within 8 hr)	38 mg/mL	VPA DC	Symptoms resolved in 3 days
		37 yo F	VPA 1200 mg/day, TPM 400 mg/day, CBZ 1000 mg/day, LMT 150 mg/day	Somnolent, dysarthric, 2 generalized tonic-clonic seizures, abnormal EEG	88 µmol/L, 3 wk after VPA started	47 mg/mL	TPM DC over 7 days; NH_4 remained ↑ and VPA was stopped	Symptoms improved after 7 days and NH4 normalized after 2 wk
Cheung et al[7]	1	15 yo M	VPA 42 mg/kg/day, TPM 50 mg/day, CZ unknown dose,	Sleepy, ↑minor seizure frequency, irritable, ↓appetite, extreme drowsiness, normal brain MRI	61 µmol/L, 2 wk after ↑VPA, 85 µmol/L, 7 days after stopping VPA, 180 µmol/L, 2 wk after restarting VPA	Tr, 395-475 µmol/L; Pk, 774 µmol/L, (nl 347-694 µmol/L)	Stopped VPA and ↑ TPM, gave IV PHT, TPM DC after persistent ↑NH4, VPA restarted, + rechallenge and DC	Symptoms improved within 7 days off of VPA first time, Stabilized on CZ monotherapy
Gomez-Ibañez et al[8]	1	49 yo F	TPM 200 mg/day, VPA 1500 mg/day, PB 100 mg/day	Behavioral change, global disorientation, gait unsteadiness, abnormal EEG	195 µg/dL, 5 yr after treatment with TPM, VPA and PB	59 mg/mL	VPA DC	Within several hours, patient recovered completely
Longin et al[9]	3	16 mo M	CBZ 450 mg/day, VPA 450 mg/day, TPM 62 mg/day	Apathy, loss of appetite, fever, ↑ LFTs	104 µg/dL, 4 wk after starting VPA and TPM	NA	VPA and TPM DC, received carnitine 100 mg/kg	6 days later recovered
		9 yo F	VPA 1500 mg/day, FBM 1000 mg/day, TPM 110 mg/day	Alopecia, apathy, hypothermia, abnormal EEG	227 µg/dL, 8 wk after starting TPM, 117 µg/dL, with TPM rechallenge	NA	TPM DC, restarted at ↓ dose 7 wk later, TPM DC after positive rechallenge	Symptoms resolved after TPM DC
		2.5 yo M	TPM 37.5 mg/day, VPA 1800 mg/day then↑	Apathy, hypothermia, thrombocytopenia without bleeding	162 µg/dL, 6 wk after ↑VPA (previous 7 mo ago 106 µg/dL)	NA	TPM DC, 2 days later VPA DC	Patient recovered
Deutsch et al[10]	1	31 yo F	VPA 1000 mg/day, TPM 45 mg/day	Somnolent, irritable, dysarthric, ataxic, hallucination, memory disturbance	41.52mmol/L, 2 wk after starting VPA	104 mg/mL	VPA DC	Symptoms resolved 1 day later

AED, antiepileptic drug; BZP, bromazepam; CZ, clobazam; CZP, clonazepam; DC, discontinued; F, female; FBM, felbamate; LMT, lamotrigine; M, male; mo, month old; NA, not vailable; NH_4, ammonia; PB, phenobarbital; PHT, phenytoin; Pk, peak; PMD, primidone; TPM, topiramate; Tr, trough; VPA, valproic acid; yo, year old.

** Six patient cases were reported, but one patient was not receiving VPA and TPM at the same time.*

Table. Reported Cases of Valproic Acid- and Topiramate-Associated Hyperammonemic Encephalopathy (*cont.*)

Study ref.	No. of Patient Cases	Patient Age	AEDs	Symptoms	NH_4 Serum Concentrations	VPA Serum Concentrations	Drug Regimen changes	Outcome
Latour et al[11]	5*	29 yo F	TPM 200 mg/day, VPA 3500 mg/day, LMT 200 mg/day, CZP 12 mg/day	↓ Appetite, weakness, ↓ seizure	62 µmol/L, 2 months after adding TPM	NA	VPA ↓to 2500 mg/day	By 2 months, recovery of general status, no change in epilepsy.
		32 yo M,	TPM 300 mg/day, VPA 2750 mg/day, BZP 0.5 mg/day,	Slow ideation, slow motor activity, fine limb tremor, weakness,↓ seizure,	65 µmol/L, 4 months after starting TPM,	105 mg/ml	VPA ↓ to 2250 mg/day, BZP ↓ to 0.25 mg/day	By 15 days, ↓ asthenia and tremor, recovered activity level, no change in seizure, By 2 months, recovery of former status
		38 yo M	TPM 300 mg/day, VPA 500 mg/day, CBZ 1200 mg/day, PMD 375 mg/day,	Drowsiness, aphasia, amnesia, apraxia, spatial disorientation, corticosubcortical neuropsychological disorder, ↓ seizures, abnormal EEG	72 µmol/L, At least 6 months after starting TPM	38 mg/ml,	TPM initially ↓ to 300 mg/day, but symptoms persisted and, VPA was weaned	By 1 month, somnolent but progressive recovery to prior status, seizure still present although EEG improved
		41 yo M	VPA 2000 mg/day, TMP 700 mg/day, CBZ 200 mg/day, LMT 200 mg/day, CZ 60 mg/day	Slow ideation, slow motor activity, asterixis. seizure cluster, abnormal EEG	146 µmol/L, 5 days after VPA was added to drug regimen, 104 µmol/L 6 days later	98 mg/ml	TPM DC and VPA ↓to 1500 mg/day	By 6 days, clinical improvement, EEG improvement, disappearance of asterixis, no cluster, By 2 months, return to baseline
		17 yo M	TPM 600 mg/day, VPA 1500 mg/day, PHT 150 mg/day, CZP 6 mg/day	Drowsiness, no effect on seizure	10 µmol/L, 10 days after adding VPA	65 mg/ml	TPM ↓ but 5 days later symptoms progressed, then TPM and PHT DC	By 4 days, clinical improvement, By 1 month, return to baseline
Vivekanandan et al[12]		5 yo M	TPM 5 mg/kg, VPA 30 mg/kg, CBZ 25 mg/kg, LEV 75 mg/kg, PB 1.5 mg/kg, LMT 2.5 mg/kg, CZP 1 mg/day	↑Seizures, drowsiness, lethargy, altered sleep/wake cycle, impaired cognition, ↓ appetite	117 µmol/L, 43 µmol/L 7 days after stopping VPA	NA	VPA DC, tapered CBZ, TPM, and PB; 10 day course of levocarnitine	By 1 week, ↓ seizures, ↑ appetite and alertness, By 3 months, ↓ seizures, ↑ weight

AED, antiepileptic drug; BZP, bromazepam; CZ, clobazam; CZP, clonazepam; DC, discontinued; F, female; FBM, felbamate; LMT, lamotrigine; M, male; mo, month old; NA, not vailable; NH_4, ammonia; PB, phenobarbital; PHT, phenytoin; Pk, peak; PMD, primidone; TPM, topiramate; Tr, trough; VPA, valproic acid; yo, year old.

** Six patient cases were reported, but one patient was not receiving VPA and TPM at the same time.*

respond despite increased levetiracetam dosing. Approximately 2 weeks prior to admission, her neurologist discontinued the levetiracetam and began delayed release VPA, 500 mg twice a day (20 mg/kg/day; usual recommended starting dose is 10-15 mg/kg/day) with lorazepam, 1 mg, as needed for seizures. During that time, she was living with "mom's friend" since her parents were separated. She also had a history of substance abuse, smoked marijuana daily and one pack of cigarettes daily, but denied any alcohol use (she had stopped when she developed JME).

On the day of admission, the patient was riding to work with a friend and was smoking a "blunt" (presumed to be marijuana). When she thought she was experiencing an aura that usually precedes her seizures, she took 1 mg lorazepam orally. At an undetermined time after the patient took her lorazepam, she became disoriented and was brought to an outside hospital ED. Upon arrival at the ED, she was noted to have a decreased sensorium and increased lethargy and was confused. Physical examination was unremarkable with the exception of hypotension (blood pressure, 86-102/52-60 mm Hg), bradycardia (heart rate, 45-70 beats per minute [bpm]) for which she received a normal saline bolus intravenously. A computed tomography scan of her head was obtained and was read as normal. Results of a complete blood count and urinary analysis were within normal limits; however, a basic metabolic panel showed mild non-anion gap hyperchloremic acidosis (Cl^-, 118 mEq/L; CO_2, 18 mEq/L). A urine drug screen result was positive for marijuana, and her serum VPA concentration was 86 mg/L. Electrocardiogram (EKG) test showed a high-normal to prolonged QTc of 443 to 459 ms. Because of her medical history, persistent symptoms, and prolonged QTc, she was transferred to our PICU for further management.

Upon arrival at the PICU, she was somnolent but would awake to verbal stimuli. She was occasionally confused during conversation and had significant speech latency but no motor or sensory deficits were observed. Her vital signs were heart rate, 61 bpm; blood pressure, 81/48 mm Hg; respiratory rate, 12 breathes per minute; and temperature, 36.6°C. The patient denied ingesting any prescription and/or over-the-counter medication, overdosing of currently prescribed medications, or suicidal/ homicidal ideations although she had a history of cutting. Initially, her home medications of TPM and VPA, twice a day at 09:00 AM and 9:00 PM, were continued. Laboratory studies were repeated approximately 8 hours after the ED tests and revealed worsening non-anion gap acidosis (Cl^-, 121 mEq/L; CO_2 , 14.5 mEq/L) that was attributed to topiramate. Her liver function test results (total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) and ionized calcium were normal. Given her persistent altered mental status, a blood ammonia concentration was obtained and was found to be elevated at 94 µmol/L (normal, 11-51 µmol/L). A repeated blood ammonia analysis 6 hours later showed a concentration of 252 µmol/L. She was given 30 grams of lactulose for hyperammonemia and the repeated blood ammonia concentration 6 hours later was 187 µmol/L. Given her elevated ammonia concentration, VPA was discontinued after her evening dose. She was monitored with telemetry while in the PICU, and over the course of the first day, her QTc ranged from 462 to 496 ms, and her heart rate ranged from 46 to 85 bpm.

On the morning of hospital day 2, the patient continued to have an altered mental status consisting of lucid intervals where she returned to her neurologic baseline, followed by somnolence and confusion. Her ammonia concentration was rechecked at 24 hours after admission and was elevated at 212 µmol/L. After receiving her morning TPM dose, the drug was held. Her morning serum VPA concentration was 64 mg/L. An electroencephalography (EEG) study showed generalized spikes plus generalized slowing, which was consistent with JME and encephalopathy. The administration of levocarnitine was recommended if the blood ammonia concentration remained elevated. Child and adolescent psychiatry was consulted due to the patient's history of substance abuse and depression and recommended outpatient counseling. As the day progressed, the patient's neurologic status continued to improve. Blood ammonia concentrations obtained 30 and 36 hours post-PICU admission were 118 µmol/L and 102 µmol/L, respectively.

By hospital day 3, her blood ammonia continued to trend downward and was 88 µmol/L at 48 hours post-PICU admission. The non-anion gap acidosis showed slight improvement (Cl^-, 118 mEq/L; CO_2 , 15.8 mEq/L), and her serum VPA concentration was 16 mg/L. She returned

to her neurologic baseline and was alert and oriented ×3 and did not have any evidence of clinical seizures. At that time, it was felt to be safe to restart a smaller dose of delayed release VPA, 250 mg twice a day, along with levocarnitine, 330 mg three times a day. Her blood ammonia concentration on day 4 was 23 µmol/L. The patient remained stable, a repeated EKG showed a normal QTc, and her vital signs remained stable. She was discharged on VPA therapy with levocarnitine and was to follow-up with neurology. A serum carnitine profile had been ordered from blood drawn on hospital admission day 2, corresponding to her ammonia concentration of 212 µmol/L, and the results available postdischarge indicated a normal serum carnitine (total, 44 nmol/mL [normal, 34-77 nmol/mL]; free, 37 nmol/mL [normal, 22-65 nmol/mL]; acylcarnitine, 7 nmol/mL [normal, 4-29 nmol/mL]).

DISCUSSION

This patient presented to our hospital with new onset hyperammonemic encephalopathy without hepatotoxicity following recent addition of VPA to her home regimen of TPM therapy, which was being given for management of JME. The encephalopathy was suspected to be due to the hyperammonemia that was probably associated with a drug-associated interaction/side effect. It was not felt to be the result of VPA overdose, especially because her VPA serum concentration on admission was within the therapeutic range. Her VPA was rapidly initiated at a moderately elevated dose, and the combination of VPA and TPM has been associated with hyperammonemic encephalopathy. Based on the Naranjo adverse drug reaction probability scale,[20] there is a possible relationship (score = 4) between the use of VPA and TPM and the development of hyperammonemic encephalopathy. This case is similar to several other cases reported in the literature (Table) in that elevated ammonia concentrations occurred after a recent change in a patient's antiepileptic drug (AED) regimen that included VPA.

The prevailing opinion in medical literature attributes VPA-associated hyperammonemic encephalopathy to a VPA-induced decrease in cellular carnitine. We obtained a serum carnitine concentration at the time of the patient's elevated blood ammonia concentration in order to refine an acute treatment strategy for this patient and found the concentrations within normal values (see above). Neither the total nor free carnitine nor acylcarnitine concentration was abnormal, suggesting alternate pathways may be greater contributing factors for the observed accumulation of ammonia (see below).

VPA is metabolized via multiple pathways, with only a small percentage, ~3%, eliminated unchanged in the urine. The majority of the drug (80%) is glucuronidated, while the remaining 17% to 20% undergoes oxidative metabolism[3] (Figure 1). This remaining portion is either metabolized in the mitochondria and proceeds through β-oxidation (70%), or undergoes ω-oxidation (30%). Most published experiences suggest that much of VPA-associated toxicity is probably the result of carnitine deficiency. Thus, the β-oxidation pathway would appear to be a very important pathway as multiple mechanisms can contribute to decreased carnitine concentrations,[1,3,13] including urinary excretion of valproylcarnitine, decreased tubular reabsorption of free carnitine and acylcarnitine, valproylcarnitine's inhibition of the carnitine transporter, decreased free fatty acid (FFA) metabolism leading to decreased production of ATP and decreased ATP-dependent carnitine transporter function, and decreased restoration of carnitine from acylcarnitine. VPA also impairs γ-butyrobetaine hydroxylase enzyme activity, possibly by decreased concentrations of the coenzyme α-ketoglutarate that is necessary for carnitine synthesis.[14]

Carnitine is critical for FFA transport into the mitochondria and indirectly affects the function of the urea cycle.[3] Deficiencies in carnitine shunt VPA metabolism more toward ω-oxidation, resulting in increased VPA toxic metabolites; other AED may induce the ω-oxidation pathways, increasing the amount of cellular and VPA-associated toxic metabolites.[11] Propionic acid metabolites and 4-en-VPA inhibit carbamyl phosphate synthetase (CPS-I), an enzyme that facilitates the conversion of NH_4^+ and HCO3$^-$ to carbomyl-P[3] (Figure 1).

Patients receiving TPM might have a decrease in HCO_3^- available because of the drug's carbonic anhydrase inhibition activity, which could also affect this conversion of NH_4^+ and HCO3$^-$ to carbomyl-P[3]. *N*-acetyl glutamic acid (NAGA), which is necessary for synthesis of CPS-I, is decreased because of decreased acetyl-CoA production from FFA metabolism. Both of the mechanisms

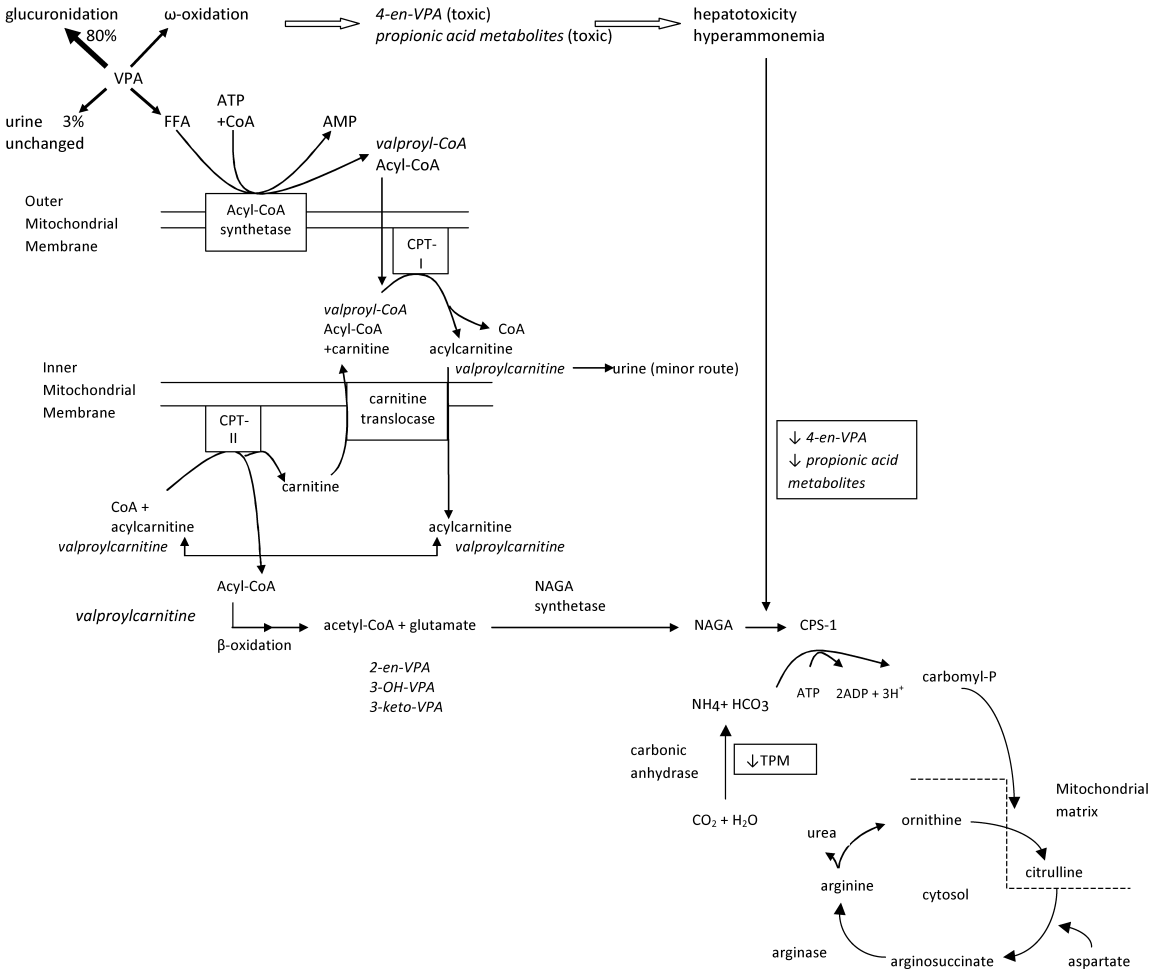

Figure 1. The Metabolic Pathways of Valproic Acid.
VPA is primarily metabolized through glucuronidation while the β-oxidation and ω-oxidation pathways account for <20% of its metabolism. The VPA metabolites are primarily responsible for VPA's toxic effects and impaired function of the urea cycle. It is proposed that when carnitine concentrations are decreased, ω-oxidation increases (usually 30% of oxidation pathways) and β-oxidation decreases (usually 70% of oxidation pathways) resulting in an increased production of toxic metabolites. VPA metabolites are indicted by italicize throughout the figure.

contribute to the accumulation of ammonia. Mechanistically, it would be very plausible for serum carnitine concentrations to be altered when patients are receiving VPA, underscoring the number of published reports of patients with low carnitine[4,15–17]; however, this does not appear to be true for all patients.[18]

Alternative sources of ammonia could explain why this may be the case. Ammonia is produced when glutamine is converted to glutamate via glutaminase (Figure 2), while glutamine synthetase converts glutamate and ammonia to glutamine. VPA's metabolite 4-en-VPA increases glutaminase activity in the renal cortex,[1] while VPA and TPM appear to decrease activity of glutamine synthetase in the kidneys and brain.[11] Both of the effects on the conversion of glutamate to glutamine could contribute to the increase in serum ammonia (Figure 2).

It is also important to consider that the encephalopathy that develops in a patient receiving VPA may not be directly related to serum ammonia concentrations since many patients have been described who have asymptomatic hyperammonemia while on VPA.[19] Cerebral edema can result when the 2-en metabolite of VPA accumulates in the brain[3] or with increased glutamate accumulation in the astrocytes, which leads to increased

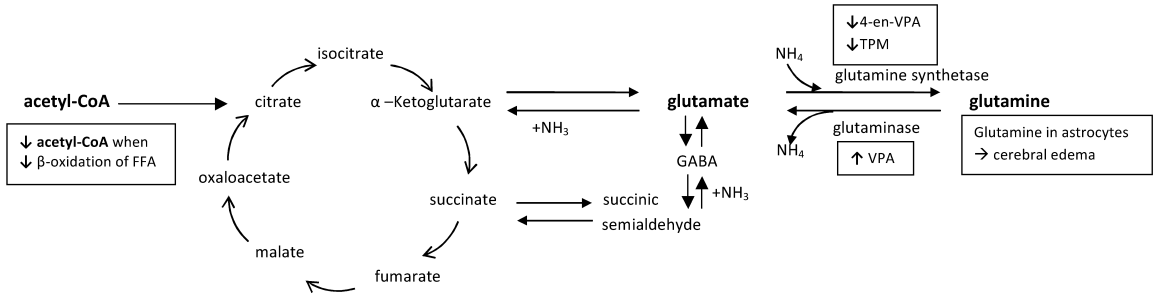

Figure 2. Synthesis and Degradation Pathways of Glutamate.
Ammonia (NH_4) concentrations may increase due to VPA increasing the activity of glutaminase while TPM and the metabolite 4-en-VPA decrease the activity of glutamine synthetase.

intracellular osmolarity and astrocyte swelling.[3] TPM is associated with cognitive impairment, especially with rapid dose titration, which may contribute to an altered mental status. Our patient had been receiving TPM without any recent dose changes for approximately 1 year prior to this acute change in her mental status; thus, it is much less likely her TPM alone was the sole factor in her acute event. Excessive inhibition of the GABA receptor by multiple drugs could also be a factor.[1] It is unclear if there are patient-specific factors or a genetic predisposition that may influence these affects in an individual.

Even though carnitine deficiency has been speculated as at least partially contributing to VPA-associated hyperammonemia and clinicians routinely consider the administration of levocarnitine to avoid or treat VPA toxicity, serum carnitine concentrations are not frequently obtained or reported in published experiences. Serum carnitine concentrations were also not reported for any of the cases of hyperammonemia encephalopathy due to VPA and TPM we identified (Table). Despite having an elevated serum ammonia, this patient had a therapeutic serum VPA concentration, and her serum carnitine profile was within normal limits. For the patient, it appears more likely that the elevated serum ammonia was due to increased renal glutaminase activity, rapid initiation of VPA and possibly decreased HCO_3^- from TPM than from overt carnitine deficiency.

The determination of serum carnitine concentrations and VPA concentrations in the face of symptomatic hyperammonia has been noted by others.[15,18] Shapira and Gutman[15] compared serum and muscle carnitine concentrations in 7 pediatric patients receiving long-term VPA therapy. Six of the patients had low muscle carnitine, but only 3 of those 6 had low serum carnitine. VPA dose and serum concentrations were not reported, although the authors stated that there was no correlation between VPA dose and the degree of carnitine depletion.[15] Hirose et al[18] measured serum carnitine concentrations in pediatric patients with epilepsy receiving VPA, with otherwise normal neurologic function and nutrition status, and found no correlation between total and free serum carnitine and serum ammonia concentrations. In fact, serum carnitine concentrations were maintained within the normal range in all the patients and were not statistically different from the control group. Thus, it can be difficult to determine what the true molecular basis of hyperammonemia and encephalopathy is for a patient given the variable laboratory results and presentations reported in the literature. It is possible that discrepancies between these studies may be due to VPA impairing cellular uptake of carnitine, resulting in apparent normal serum concentrations but low tissue concentrations, or pharmacogenomic patient differences affecting the response. It also brings into question the necessity for levocarnitine.

Even though levocarnitine is relatively safe and has been used as maintenance therapy in patients receiving VPA or in patients with VPA-associated toxicity, serum carnitine concentrations are not always affected by a patient's AED therapy, as noted in our patient. Therefore, the usefulness of levocarnitine in all patients may not be as beneficial as previously thought and should be further assessed. However, it may be difficult to determine a patient's carnitine status in the setting of acute VPA toxicity since serum/urine carnitine determination are usually not routine

laboratory tests available at most healthcare facilities, including ours, and as such, results may not be available until days later. Additionally, there may be discrepancies between serum and tissue/ muscle concentrations of carnitine. Further studies would help to assess the correlation between serum and tissue/ muscle carnitine concentrations in these patients, especially for patients receiving multiple AEDs that include VPA and in particular, VPA, TPM, and/or phenobarbital, (phenobarbital has also been linked to increased cerebral glutamine synthetase activity[1, 8]) and the role of levocarnitine. Thus, in patients with apparent VPA-associated hyperammonemia which does not readily resolve with appropriate doses of levocarnitine, an alternative etiologic metabolic pathway should be considered (e.g., renal glutaminase activity) and if continued VPA is required, the clinician should reassess the dosing regimen and/or drug interactions.

CONCLUSIONS

Our case highlights the occurrence of hyperammonemic encephalopathy following coadministration of VPA and TPM in a patient with normal serum carnitine concentrations. Multiple mechanisms have been speculated for this adverse drug effect; however, at least for our patient, it appears that decreased serum carnitine may not be as prominent of a contributing factor. More research into the possible mechanism(s) contributing to VPA-associated toxicity, and more specifically VPA-associated hyperammonemia, is clearly needed to better define specific and optimal therapies.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS AED, antiepileptic drug; bpm, beats per minute; CPS-I, carbamyl phosphate synthetase; ED, ED; EKG, electrocardiogram; FFA, free fatty acid; JME, juvenile myoclonic epilepsy; NAGA, *N*-acetyl glutamic acid; PICU, pediatric intensive care unit; TPM, topiramate; VPA, valproic acid

CORRESPONDENCE Martha Blackford, PharmD, Akron Children's Hospital, One Perkins Square Akron, OH 44308, email: mblackford@chmca.org

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