

Levocarnitine for valproate-induced hyperammonemia in the psychiatric setting: A case series and literature review

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Abstract

Introduction: Hyperammonemia is a potential adverse effect of valproic acid (VPA) therapy, which is often asymptomatic but can lead to severe, life-threatening encephalopathy. Carnitine deficiency due to VPA is the proposed mechanism for hyperammonemia and the development of VPA-induced hyperammonemic encephalopathy (VHE). Levocarnitine, the active form of carnitine, has been suggested for treatment and prevention of VHE.

Methods: Data was collected by chart review of 3 patients who received oral levocarnitine supplementation in the psychiatric setting for VPA-induced hyperammonemia. Review of the literature was performed through June 2017 using the following PubMed search terms: *valproate, valproic acid, hyperammonemia, altered mental status, encephalopathy, and levocarnitine*. Articles were included if they described use of levocarnitine in VPA-treated patients with psychiatric disorders.

Results: One patient developed encephalopathy with resolution of symptoms after VPA discontinuation. Valproic acid was restarted with the addition of levocarnitine to prevent VHE recurrence. In the other 2 cases, levocarnitine was started prophylactically in patients who developed hyperammonemia without emergence of any clinical symptoms. Ammonia levels were reduced to normal in all cases, and no symptoms consistent with encephalopathy were reported. The literature search identified 6 additional cases with 5 of 6 reports supporting use of levocarnitine for decreased ammonia levels as well as an observational trial.

Discussion: This literature review and case series illustrates successful use of levocarnitine supplementation for reduction of ammonia levels in the setting of VPA-induced hyperammonemia among patients with psychiatric disorders. However, clinical significance of ammonia reduction in asymptomatic patients is difficult to determine.

Keywords: levocarnitine, carnitine, valproate, valproic acid, encephalopathy, hyperammonemia

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Background

Valproic acid (VPA) is a branched carboxylic acid used to treat various psychiatric illnesses as well as seizure

disorders and migraines. In the psychiatric population, VPA is primarily utilized for its mood stabilizing properties and with a limited number of medications effective for this purpose, tolerability issues are an important concern. One potentially harmful adverse effect that may occur as a result of VPA treatment is hyperammonemia. Although many patients with hyperammonemia remain asymptomatic, elevated ammonia levels can lead to life-threatening VPA-induced hyperammonemic encephalopathy (VHE). Clinical symptoms of VHE have been characterized by lethargy, nausea/vomiting, cognitive slowing, focal neurological deficits, and decreased levels of consciousness, ranging from drowsiness to coma.¹⁻³

Structurally, VPA is similar to short-chain fatty acids and is a substrate for fatty acid mitochondrial β -oxidation and cytoplasmic ω -oxidation pathways. Carnitine is an essential cofactor in the metabolism of fatty acids and mitochondrial energy production. During VPA therapy, carnitine combines with VPA to form valproylcarnitine. As a minor route of elimination, valproylcarnitine is excreted in the urine. Valproylcarnitine also inhibits the membrane transporter responsible for transferring extracellular carnitine into the cell and mitochondria. Additionally, VPA metabolites trap mitochondrial coenzyme A so that carnitine cannot be restored through the action of carnitine palmitoyl transferase II. Reduced carnitine from these mechanisms results in decreased β -oxidation of VPA and shifts the metabolism toward predominately ω -oxidation, producing a toxic metabolite, 2-propyl-4-pentenoic acid (4-en-VPA). This metabolite reduces ammonia elimination through inhibition of carbamoyl-phosphate synthase I, the first enzyme in the urea cycle, thus, increasing ammonia levels.⁴

In 1989, levocarnitine (L-carnitine, active isoform of carnitine) received Food and Drug Administration orphan drug designation for the prevention and treatment of secondary carnitine deficiency in VPA toxicity.⁵ Review articles^{4,6,7} have described levocarnitine supplementation for VHE in the setting of acute valproic acid overdose. Levocarnitine has also been suggested for treatment and prevention of VHE in patients treated with usual VPA doses. However, the majority of evidence supporting this use comes from pediatric neurology literature.⁷ The present article discusses 3 cases of levocarnitine supplementation for hyperammonemia in the context of VPA treatment of psychiatric disorders and provides a review of the current literature.

Cases

Case 1

A 65-year-old male with bipolar I disorder was admitted to the inpatient psychiatry unit for an acute manic episode.

His outpatient medication regimen, past medical history, and admission labs are described in Table 1.

On admission, outpatient psychiatric medications were discontinued and VPA solution (500 mg every morning, 1000 mg every evening) and risperidone tablets (1 mg twice daily) were initiated. Valproate and risperidone were titrated to doses of 3000 mg/d and 6 mg/d, respectively, over the course of 5 days. On day 7, the patient became somnolent, which progressed to garbled speech and altered mental status. Laboratory testing revealed a VPA level of 68 $\mu\text{g/mL}$ (lab reference range: 50 to 100 $\mu\text{g/mL}$) and an ammonia level of 56 $\mu\text{mol/L}$ (lab reference range: 16 to 53 $\mu\text{mol/L}$). Valproate was discontinued with resolution of symptoms. Following VPA discontinuation, staff noted reemergence of mania symptoms, including agitation and hypersexual behaviors. On day 11 of admission, lithium 900 mg/d was initiated and VPA solution was restarted at a lower dose of 1000 mg/d, which was eventually increased to 1500 mg/d divided twice daily. At the time of VPA dose increase, levocarnitine 990 mg daily was initiated to prevent VHE and was increased 3 days later to 990 mg twice daily. Blood levels were rechecked 2 weeks later, and ammonia was found to be 23 $\mu\text{mol/L}$ and the VPA level was 50 $\mu\text{g/mL}$. No symptoms of encephalopathy were reported during the admission after levocarnitine was started.

Valproate was continued as an outpatient but for reasons unknown, levocarnitine was not renewed. Approximately 3 months after inpatient discharge, the patient was admitted to the hospital for encephalopathy with an elevated ammonia level of 66 $\mu\text{mol/L}$ and a low VPA level of 19 $\mu\text{g/mL}$ as it was held for somnolence. Valproate was discontinued and not restarted.

Case 2

A 64-year-old male with schizoaffective disorder, bipolar type, was admitted to the inpatient psychiatric unit for disorganized behavior. Outpatient medications, past medical history, and admission labs are provided in Table 1. Valproate level on admission was 82 $\mu\text{g/mL}$.

Over an 8-week hospital course, the medication regimen was gradually changed to VPA solution 1250 mg every morning and 1500 mg at bedtime, haloperidol 5 mg twice daily, clonazepam 1 mg at bedtime. Valproate level was found to be 141 $\mu\text{g/mL}$ (7.5-hour post-dose level at steady state; true trough calculated to be ~ 88 $\mu\text{g/mL}$) and ammonia was elevated at 63 $\mu\text{mol/L}$, increased from 47 and 49 $\mu\text{mol/L}$ earlier in the admission. No changes in mental status were noted with elevated ammonia. Levocarnitine 990 mg was given once. Ten hours later, ammonia decreased to 44 $\mu\text{mol/L}$ and 13-hour post-dose VPA level was 64 $\mu\text{g/mL}$. The patient was discharged on

TABLE 1: Case series patient information

	Case 1	Case 2	Case 3
Admission labs and reference range			
WBC			
4 to 10 10 ³ /μL	16.1	10.7	9.8
HGB			
13.5 to 17.5 g/dL	12.5	12.4	14.4
PLT			
150 to 400 10 ³ /μL	254	170	334
Na			
136 to 145 mmol/L	138	142	136
K			
3.5 to 5.1 mmol/L	4.3	3.5	4.8
Cl			
98 to 107 mmol/L	101	108	103
CO ₂			
21 to 31 mmol/L	30	22	29
BUN			
7 to 25 mg/dL	20	19	20
SCr			
0.7 to 1.3 mg/dL	0.8	0.8	1.0
Glu			
70 to 105 mg/dL	143	266	90
AST			
13 to 39 IU/L	22	35	46
ALT			
7 to 52 IU/L	22	31	36
TBili			
0.3 to 1 mg/dL	0.4	0.3	0.5
Albumin			
3.5 to 5.7 g/dL	3.8	3.8	4.0
Outpatient medications	<ul style="list-style-type: none"> • Aripiprazole 5 mg PO QAM • Paliperidone LAI 156 mg IM every 4 wk • Mirtazapine 15 mg PO QHS • Trazodone 300 mg PO QHS • Acetaminophen 650 mg PO every 12 h PRN pain or fever • Amlodipine 5 mg PO daily • Aspirin 81 mg PO daily • Ciprofloxacin 500 mg PO BID × 7 d^a • Docusate 240 mg PO daily • Folic acid 1 mg PO daily • Guaifenesin 100 mg/5 mL 10 mL PO TID PRN cough • Metronidazole 500 mg PO QID × 7 d^a • Omeprazole 20 mg PO QAM • Propranolol 40 mg PO BID 	<ul style="list-style-type: none"> • Clonazepam 1 mg PO QAM and QHS • Diphenhydramine 25 mg PO daily, 50 mg PO QHS • Divalproex ER 2500 mg PO daily • Risperidone 2 mg PO BID • Amlodipine 5 mg PO daily • Aspirin 81 mg PO daily • Budesonide/formoterol 80/4.5 mcg 2 puffs inhaled BID • Cyanocobalamin 1000 mcg PO daily • Folic acid 1 mg PO daily • Glipizide 20 mg PO BID AC • Lisinopril 40 mg PO daily • Loratadine 10 mg PO daily • Metformin ER 1000 mg PO daily • MVI PO daily • Simvastatin 10 mg PO QHS 	<ul style="list-style-type: none"> • Buspirone 20 mg PO BID • Hydroxyzine 10 mg PO daily PRN anxiety • Lithium 600 mg PO BID • Perphenazine 8 mg PO TID • Trihexyphenidyl 2 mg PO TID • Cholecalciferol 1000 units PO daily • Fluticasone nasal spray 2 sprays BID • Gemfibrozil 600 mg PO BID • Levothyroxine 125 mcg PO QAM • Loratadine 10 mg PO daily • Metoprolol tartrate 25 mg PO BID
Past medical history	HTN, COPD, GERD, renal failure 2/2 lithium	HTN, HLD, DMII	HTN, HLD, obesity, OSA, Grave's disease s/p ablation, pancreatitis

2/2 = secondary to; AC = before meals; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BUN = blood urea nitrogen; Cl = chloride; CO₂ = carbon dioxide; COPD = chronic obstructive pulmonary disease; DMII = type II diabetes mellitus; GERD = gastroesophageal reflux disease; Glu = glucose; HCT = hematocrit; HGB = hemoglobin; HLD = hyperlipidemia; HTN = hypertension; IM = intramuscular; K = potassium; Na = sodium; OSA = obstructive sleep apnea; PLT = platelets; PO = by mouth; PRN = as needed; QAM = every morning; QHS = at bedtime; QID = 4 times daily; RBC = red blood cell; SCr = serum creatinine; TBili = total bilirubin; TID = 3 times daily; UDS = urine drug screen; WBC = white blood cell.

^aEmergency department visit, acute sigmoid diverticulitis.

levocarnitine 990 mg daily for 2 days then 990 mg twice a day to prevent hyperammonemia with chronic VPA use. Valproate solution was changed to VPA derivative, divalproex ER 2500 mg/d.

It is unclear if the patient was adherent to levocarnitine as an outpatient. Ammonia was found to be elevated at 67 and 71 $\mu\text{mol/L}$ on 2 separate occasions. The patient was readmitted to the hospital a few months later and found to have a VPA level of 70 $\mu\text{g/mL}$ on divalproex ER 2500 mg/d and an ammonia level of 75 $\mu\text{mol/L}$. After 9 days of witnessed adherence to levocarnitine 330 mg 3 times daily, ammonia level decreased to 29 $\mu\text{mol/L}$. Valproate level was 25 $\mu\text{g/mL}$ (23-hour post-dose level at steady state). The patient was discharged on levocarnitine 990 mg twice daily to be continued with divalproex.

Case 3

A 53-year-old acutely manic male with bipolar I disorder and substance use disorder was transferred from an outside hospital. Outpatient medications, past medical history, and labs after transfer are reported in Table 1.

The patient was continued on the medications from the outside hospital. During his admission at our facility, the patient was briefly transferred to the medicine service due to hypernatremia, which the medicine team attributed to lithium and stopped the medication. At time of transfer back to the psychiatric unit, the patient was initiated on VPA solution 1000 mg twice daily. Over the next 4 days, ammonia levels were found to be elevated at 59, 65, and 82 $\mu\text{mol/L}$. Once at steady state, VPA level was 104 $\mu\text{g/mL}$. Manic symptoms persisted but no changes in mental status were noted. Despite lack of symptoms, lactulose was started for hyperammonemia and given for 3 days. Two days after lactulose was initiated, levocarnitine was also started at 1000 mg daily for 3 days then increased to twice daily. Ammonia levels decreased but remained elevated during the 2 weeks following levocarnitine initiation at 70, 58, 67, and 68 $\mu\text{mol/L}$. Levocarnitine was then increased to 1000 mg every morning and 1500 mg every evening during the second week to target hyperammonemia. After 3 weeks, ammonia levels were checked every 8 to 10 days and found to be within normal range or slightly elevated at 46, 46, 59, and 49 $\mu\text{mol/L}$. The patient was discharged on VPA and levocarnitine. Similar to our second case, it was unclear if the patient was adherent to levocarnitine as an outpatient. He was readmitted to our psychiatry unit again and found to have a VPA level of 115 $\mu\text{g/mL}$ and an ammonia level of 74 $\mu\text{mol/L}$, which decreased to 30 $\mu\text{mol/L}$ after levocarnitine supplementation.

Literature Review

A PubMed search was performed through June 2017 with search terms including *valproate*, *valproic acid*, *hyperammonemia*, *altered mental status*, *encephalopathy*, and *levocarnitine*. References of articles obtained from the search were also screened for inclusion. In this review, we present only relevant medical literature assessing VPA-treated patients with psychiatric disorders. To summarize results that are applicable to the patients in our case series, reports describing valproic acid use for epilepsy were not included.

Forty-four cases of VHE in the psychiatric setting were identified^{1,8,10-18} along with 1 report of asymptomatic hyperammonemia with long-term VPA therapy.⁹ Of these cases, 6 described the use of levocarnitine^{9,15-18} and are summarized in Table 2. Presented patients had VPA levels that ranged from 73 to 120 $\mu\text{g/mL}$ and elevated ammonia levels that ranged from 96 to 377 $\mu\text{mol/L}$. Clinical presentation ranged from asymptomatic to mild lethargy to coma. Levocarnitine was given by intravenous route in 2 cases at doses of 100 mg/kg and 3 g, respectively. Authors¹⁵⁻¹⁸ observed a decrease in ammonia levels within 6 to 7 hours of IV administration. Levocarnitine oral supplementation doses ranged from 1500 to 2970 mg/d divided 2 to 3 times daily. Five of the 6 case reports described decreased ammonia levels and resolution of symptoms (if any) with levocarnitine use. Valproate was continued in 3 of the cases in the setting of decreased ammonia levels with levocarnitine supplementation. However, Young and Coffey¹⁸ described a pediatric patient who had persistent ammonia elevations when VPA was continued despite levocarnitine oral supplementation up to 1500 mg/d divided twice daily.

One observational study¹⁹ was identified that examined the effect of levocarnitine supplementation (30 mg/kg body weight daily, route not reported) in VPA-treated patients ($n = 22$) with continuous hyperammonemia ($\text{NH}_3 > 50.5 \mu\text{mol/L}$) for at least 3 months. All patients were receiving psychiatric care (inpatient or outpatient not specified) at Kusatsu Hospital in Hiroshima, Japan and followed prospectively from September 2013 to June 2014. The authors made no comment on whether the patients experienced symptoms of encephalopathy at baseline or any point throughout the duration. They found that levocarnitine led to a significant increase in mean total carnitine levels after 3 months of supplementation. Ammonia reduction from baseline over 3 months was observed in over half (12/22) of participants. However, the mean ammonia level at 3 months was not significantly different from baseline.

Discussion

Hyperammonemia may be a relatively common adverse effect of VPA in patients with psychiatric disorders based

TABLE 2: Levocarnitine for VPA-induced hyperammonemia, cases in psychiatric setting

Author	Age	Sex	DSM	Clinical Picture	VPA Dose, mg/d	VPA, µg/mL	NH ₃ , µmol/L	Treatment	Outcome	VPA D/C?
Case series										
Patient 1	65	M	BD	AMS resolved after VPA D/C then restarted	3000 then ↓ to 1500	68	56	Levocarnitine 990 mg PO daily × 3 d then 990 mg PO BID	Sxs did not recur, NH ₃ level 50	No
Patient 2	64	M	SAD	No sxs	2750	141	63	Levocarnitine 990 mg PO daily × 3 d then 990 mg PO BID	No sxs emerged, NH ₃ level 44 within 10 h	No
Patient 3	53	M	BD	No sxs	2000	104	82	Levocarnitine 1 g PO daily × 3 d then 1 g PO BID × 2 wk then 1 g QAM, 1.5 g QHS	No sxs emerged, NH ₃ level ↓ to WNL over 3 wk	No
Literature review										
Aiyer et al ⁹	58	F	BD	No sxs	2000	117	225	Lactulose 20 g PO BID, levocarnitine 990 mg PO TID	NH ₃ level ↓ to 163 then 27 within 2 wk	No
Barrueto and Hack ¹⁵	41	M	BD	Lethargy, AMS, vomiting, coma	NR; same dose × 3 y	73.5	377	Activated charcoal, levocarnitine 100 mg/kg IV × 1	NH ₃ level ↓ to 47 within 7 hrs, sxs resolved within 24 h	Yes
Eubanks et al ¹⁶	33	F	BD PTSD BPD	Lethargy, AMS	1500	120	283	Levocarnitine 3 g IV followed by 990 mg PO BID, lactulose 30 mL PO every 6 h × 7 d	NH ₃ level ↓ to 41, sxs resolved within 6 h; 66, 30, 25 on next d	Yes
Raby ¹⁷	24	F	BPD MDD	Lethargy, fatigue, persistent nausea	1000 then ↓ 750	89.9 ^a	102 then 51	Levocarnitine 1 g PO BID	NH ₃ level ↓ to 28, sxs resolved within 10 d	No
Raby ¹⁷	38	F	BD	Cognitive slowing, lethargy	1000	73 ^a	101	Levocarnitine 1 g PO BID	NH ₃ ↓ to 22, sxs resolved within 2 wk	No
Young and Coffey ¹⁸	15	M	BD	Sedation, lethargy	1750 then ↓ to 1500	100	96	Levocarnitine 500 mg PO BID then ↑ to 750 mg PO BID	Persistent NH ₃ elevations, VPA eventually D/C after failed trial of levocarnitine	No

AMS = altered mental status; BD = bipolar disorder; BID = twice daily; BPD = borderline personality disorder; D/C = discontinued; DSM = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) diagnosis; F = female; IV = intravenously; M = male; MDD = major depressive disorder; NH₃ = ammonia; NR = not reported; PO = by mouth; PTSD = posttraumatic stress disorder; QAM = every morning; QHS = at bedtime; QPM = every evening; SAD = schizoaffective disorder; sxs = symptoms; TID = 3 times daily; VPA = valproic acid; WNL = within normal limits.

^aReported in µmol/L in case report, unclear if units are correct given that conversion puts levels at 12.9 and 10.5 µg/mL (below therapeutic range)

on prospective studies.^{20,21} One study²⁰ found that 51% of VPA-treated patients had asymptomatic hyperammonemia compared to 21.7% of patients taking other mood stabilizers. While often asymptomatic, elevations in ammonia can progress to VHE. Risk factors associated with VHE include age less than 2 years, therapy with multiple antiepileptic drugs, developmental disability, vegan/vegetarian diets, and urea cycle disorders.^{1,7,16} Phenytoin, phenobarbital, carbamazepine, and topiramate interact with VPA and may also precipitate VHE.¹ Prevalence of VHE in patients with hyperammonemia is unknown. In 1 retrospective study²² of VPA-treated patients with psychiatric disorders and hyperammonemia during a 5-year period, only 20 of 793 (2.52%) patients had symptoms consistent with VHE.

Based on the literature reviewed, several case reports suggest that levocarnitine may be effective for reduction of ammonia levels in patients with psychiatric disorders on VPA therapy. In addition, the highest quality evidence available from our literature search was described in a single prospective, observational trial examining ammonia levels in VPA-treated patients after 3 months of levocarnitine supplementation.¹⁹ In this study, levocarnitine was effective in decreasing ammonia levels in over half of the participants. While mean ammonia level at the end of the study was not significantly different from baseline, ability to detect a difference may have been limited due to the small sample size. In this observational cohort as well as the case reports described, lack of a placebo comparator makes it impossible to ascertain whether decreased ammonia levels are associated with levocarnitine supplementation rather than the result of normal physiologic changes.

In our series of 3 cases, we also described levocarnitine supplementation in the psychiatric setting for VPA-induced hyperammonemia, which resulted in reduced ammonia levels. In our first case, the patient developed encephalopathy with resolution of symptoms after VPA discontinuation. Valproate was restarted with the addition of levocarnitine to prevent VHE from reoccurring. In the other cases, levocarnitine was started as a prophylactic measure in patients who developed hyperammonemia without emergence of any clinical symptoms.

Levocarnitine is supplied as an oral preparation (1g/10 mL solution, 330 mg tablets, 500 mg tablets) and an intravenous preparation (2 g/10 mL).²³⁻²⁵ Levocarnitine was dosed at a range of 1980 to 2500 mg divided twice daily in patients from our cases series, which was consistent with case reports from the literature review. The manufacturer recommended dosing approved by the Food and Drug Administration for levocarnitine oral supplementation for primary and secondary (inborn error of metabolism) carnitine deficiency is 990 mg 2 to 3 times

daily for tablets and 1 g 2 to 3 times daily for solution.^{23,24} Intravenous levocarnitine is indicated for carnitine deficiency secondary to metabolic disorders and in end stage renal disease.²⁶

Levocarnitine was well tolerated in our patients with no adverse effects. Common adverse effects reported with levocarnitine include nausea, dose-related diarrhea, and fishy body odor.⁷ Although generally well tolerated, it is important to consider clinical need for levocarnitine. Patients with VPA-induced hyperammonemia are often asymptomatic and clinical significance of ammonia reduction in these patients is difficult to determine. Nonadherence to levocarnitine and discontinuation by outpatient providers may also affect maintenance of normal ammonia levels as evidenced by elevated ammonia levels upon readmission in our patients.

Carnitine levels were not obtained in our patients. Hypocarnitinemia may be a more compelling indication for levocarnitine supplementation in cases of hyperammonemia without clear clinical symptoms. In a retrospective chart review of psychiatric patients, 38 patients were identified as having documented hypocarnitinemia and being prescribed levocarnitine (mean dose 660 mg/d, mean duration 6.4 months) with 71% of these patients prescribed VPA. After correction of carnitine levels, Mini-Mental State Examination scores improved in most patients (mean improvement 5.5 points, $P < .0001$), and normalized in 11 cases.²⁶ This finding was supported by another study¹⁹ that showed improvement in the mental retardation item of the Brief Psychiatric Rating Scale after 3 months of levocarnitine supplementation in patients with VPA-induced hyperammonemia.

In addition to hypocarnitinemia, other risk factors for VHE in the psychiatric setting should be examined in future studies. Determination of risk factors may help clinicians identify patients who may benefit from levocarnitine supplementation with long-term VPA therapy to prevent VHE.

Conclusion

Although limited to case reports and an observational trial, available evidence suggests that levocarnitine may be effective for decreasing elevated ammonia levels in patients with psychiatric disorders on VPA therapy. This case series illustrates successful use of levocarnitine supplementation for reduction of ammonia levels in the setting of VPA-induced hyperammonemia. Although these 3 patients did not develop encephalopathy while on levocarnitine supplementation, clinical significance of ammonia reduction in asymptomatic patients is unclear. Consideration of risk factors, including carnitine status

may be important for selecting patients who may benefit from supplementation.

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