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Valproate, risperidone, and paliperidone: A case of valproate-induced hyperammonemic encephalopathy

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Abstract

Hyperammonemia is a well-known adverse effect of valproate that can progress to a potentially fatal condition known as valproate-induced hyperammonemic encephalopathy (VHE). VHE is more common when valproate is used in combination therapy with other antiepileptic medications. A growing number of case reports have pointed to a possible interaction with the antipsychotic risperidone leading to an increased risk of VHE. We present a case of VHE in which a 20-year-old male patient with bipolar affective disorder developed VHE when on concomitant valproate, risperidone, and paliperidone palmitate. On the seventh day of treatment with oral risperidone, oral divalproex sodium was added. Intramuscular paliperidone palmitate was initiated on day 13, and oral risperidone was discontinued after the second loading dose on day 16. The following day, the patient displayed worsening psychomotor retardation, swaying gait, drowsiness, and vomiting. The patient was found to have hyperammonemia and transferred to the emergency department for treatment of suspected VHE.

Keywords: valproate, encephalopathy, VHE, risperidone, paliperidone palmitate

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Background

Hyperammonemia is a well-documented adverse effect of valproate (VPA) with a wide estimated prevalence between 2% and 80%.[1] Most cases are asymptomatic, but symptoms may occur in 0.7% to 22% of patients.[2] VPA-induced hyperammonemic encephalopathy (VHE) develops in 0.1% to 2.52% of cases.[3] Symptoms of VHE include confusion, lethargy, neurologic deficits, and coma.[1] Risk factors include concomitant antiepileptic drugs, urea cycle disorders, and carnitine deficiency.[1,4] Antipsychotics have displayed an increased risk of hyperammonemia when used in combination with VPA.[1] The mechanism of VHE is related to the hepatic metabolism of VPA through glucuronidation, β-oxidation, and ω-oxidation.[4] VPA inhibits the biosynthesis of carnitine, an essential cofactor in β-oxidation, leading to carnitine deficiency.[4] Carnitine deficiency reduces metabolism via β-oxidation, increasing the amount of VPA metabolized via ω-oxidation. The resulting metabolites inhibit the urea cycle, leading to increased ammonia, which causes encephalopathy.[4] Common treatments of VHE include discontinuation of VPA, carnitine supplementation, and lactulose.[4,5] The following case describes a patient who develops VHE during the concomitant use of VPA, risperidone, and paliperidone palmitate.

Case Report

A 20-year-old male was admitted to the inpatient psychiatry unit with symptoms of bipolar disorder, type I, current

episode mania with psychosis. His only home medication was oral paliperidone with questionable adherence. Benztropine and risperidone were initiated and titrated to 1 mg daily and 4 mg daily, respectively, with minimal improvement. As-needed doses of oral and/or intramuscular haloperidol, olanzapine, lorazepam, and diphenhydramine were given to treat his aggressive behavior. Oral divalproex sodium delayed release was added on day 7 of treatment and titrated to 750 mg twice daily. He became more organized and less aggressive with steady improvement in his manic and psychotic symptoms. The patient reported transient tinnitus, lasting 24 hours. A steady-state VPA concentration (91 μg/mL) was measured on day 12. Due to a history of poor medication compliance, a paliperidone palmitate load (234 mg) was administered on day 13. Oral risperidone was continued until the second loading dose (156 mg) was given on day 16. On the days between paliperidone palmitate doses, the patient displayed hypersalivation, mild cogwheel rigidity, vomiting, and drowsiness. Liver function tests (LFTs) were obtained and were within normal limits (WNL) except for slightly elevated alanine aminotransferase at 51 U/L and total bilirubin at 1.8 mg/dL. Baseline labs for comparison were unavailable. After the second loading dose, he displayed worsening psychomotor retardation with an unsteady gait and inability to grasp a cup of water, continued drowsiness, and incoherent speech. Repeat LFTs (WNL) and an ammonia concentration (379 μg/dL) were ordered. On day 17, he was transferred to the emergency department with suspected VHE. An ammonia concentration obtained 6 hours later was 84 μg/dL despite no interventions. His VPA concentration was 78 μg/mL, and free VPA was 5.8 mg/L. A third ammonia concentration (234 μg/dL) was obtained 10 hours later, prompting medical admission. VPA and benztropine were held and lactulose 20 g oral solution 3 times daily was initiated. On day 18, his ammonia concentration was 180 μg/dL, which trended down to 77 μg/dL the following day when he was deemed medically stable. Throughout treatment for VHE, his albumin levels were WNL, ranging from 3.8 to 4.4 g/dL. Upon readmission to the psychiatric unit, VPA and benztropine were not resumed, and he was initiated on lithium, titrated over 1 week, and discharged on intramuscular paliperidone palmitate 156 mg monthly, oral lithium carbonate extended release 450 mg at bedtime, and trazodone 50 mg at bedtime as needed for sleep.

Discussion

This case adds to existing literature linking concomitant VPA and risperidone therapy to VHE. Multiple published cases of symptomatic VHE have involved this combination of medications (Table).[6–13] Of note, this patient was initiated on paliperidone palmitate when taking risperidone and VPA. As an active metabolite of risperidone, it is possible that paliperidone shares a risk of VHE.

Previous reports associating paliperidone palmitate and VHE are scarce. A case study reported a case of VHE in a 29-year-old with schizoaffective disorder treated with paliperidone palmitate and VPA semisodium.[10] The patient was prescribed VPA semisodium and paliperidone extended release for several years. After a relapse, the patient was admitted with suspected noncompliance to VPA. VPA was initially restarted but switched to lithium. The patient developed acute confusion with an ammonia concentration of 183 μmol/L and diagnosed with VHE. The precipitant of VHE in this case was concluded to be a drug interaction with lithium.

Most instances of VHE are reversible, but it can be fatal.[11,14] The relationship between VHE, VPA dose, VPA blood concentration, and ammonia concentration is controversial. Some evidence suggests blood concentration of ammonia is correlated with both the dose and blood concentration of VPA, and most cases of VPA-induced hyperammonemia are asymptomatic.[1] A review of 14 VHE cases found no correlation between ammonia concentration, VPA concentration, and severity of clinical symptoms.[14] Many patients with VHE have therapeutic blood concentrations of VPA and normal hepatic transaminase levels.[3,14] The initial presentation of VHE varies and can include slurred speech, ataxia, lethargy, persistent nausea, inappropriate behavior, tremor, sedation, and cognitive impairment.[14] Acute encephalopathy may present with alterations in consciousness and behavioral changes.[3] Behavioral changes, such as psychosis or irritability, may be more difficult to attribute to VHE in patients with mood or psychotic symptoms as changes may be secondary to the underlying condition. VHE may also present as cognitive impairment and reversible Parkinson disease.[3] The onset of VHE varies with respect to duration of therapy, ranging from days to years.[11,14] Hyperammonemia is more common in patients treated with combination therapy, especially with concomitant use of phenytoin and topiramate.[1,15] Additionally, a study examining risk factors for VPA-induced hyperammonemia found that 7 of 10 patients on dual therapy with antipsychotics and VPA developed hyperammonemia ($P = .011$).[1] The antipsychotics included in this study were aripiprazole, sulpride, amisulpride, risperidone, paliperidone, and quetiapine. Authors did not report on rates of hyperammonemia associated with the individual combinations. The patient in the current case had no known carnitine deficiency or urea cycle disorders and was not taking any other medications associated with VHE. Polypharmacy with risperidone and paliperidone was his only known risk factor for VHE.

A previously proposed mechanism of the interaction between risperidone and VPA is speculated to involve the relative protein binding properties of these drugs.[7,16] Both drugs are highly protein bound such that risperidone may displace VPA.[16] The protein binding of VPA is concentration dependent with a free

TABLE: Summary of cases of VHE involving risperidone and paliperidone palmitate

Case	Patient	Diagnosis	Medications	Onset	Serum VPA	Serum Ammonia
Davoudi-Monfared et al (2019)[6]	35 yo F	Schizophrenia	VPA 1000 mg in divided doses; risperidone 4 mg daily	10 days after risperidone added to VPA	128 mg/L	297 µg/dL (day 20)
Davoudi-Monfared et al (2019)[6]	49 yo F	Bipolar disorder	VPA 500 mg TID; risperidone 2 mg BID	4 days after risperidone dose increase	201 µg/mL	327 µg/dL
Carlson et al (2007)[7]	11 yo M	Asperger disorderand ADHD	VPA 750 mg; risperidone 3 mg	Within 1 week of VPA added to risperidone	87 to 90 µg/mL	213 µg/dL
Carlson et al (2007)[7]	11 yo M	Epilepsy and ADHD	VPA; risperidone 1.125 mg daily	3 to 4 weeks after initiating risperidone titration	71 µg/mL	113 µg/dL
Baumgartner et al (2019)[8]	26 yo M	Acute mania	VPA 2500 mg daily; risperidone 8 mg daily	14 days after initiation of VPA and risperidone	1023 µmol/L	412.2 µmol/L
Rodrigues-Silva et al (2013)[9]	41 yo F	Manic episode	VPA 1000 mg/day; risperidone 4 mg/day	6 days after adding VPA to risperidone	94.5 µg/mL	213.4 µg/dL
Levy et al (2022)[10]	29 yo M	Schizoaffective disorder	VPA 2000 mg daily; paliperidone ER 100 mg every 28 days; lithium 400 mg daily	3 days into a cross-taper from VPA to lithium	130 mg/L	182 µmol/L
Chopra et al (2011)[11]	36 yo M	Schizoaffective disorder, bipolar type	VPA 1000 mg daily; risperidone 3 mg/day	1 week following addition of VPA	114 µg/mL	111 µmol/L
Carr and Shrewsbury (2007)[12]	45 yo F	Schizoaffective disorder, bipolar type	VPA 1500 mg daily; risperidone 3 mg BID	10 days following addition of risperidone to VPA	141 µg/mL	445 µg/dL
Vaidyanathan et al (2023)[13]	75 yo F	Schizoaffective disorder, manic episode	VPA 800 mg daily; risperidone 7 mg daily	8 days of VPA use	Not available	102 µg/dL
Vaidyanathan et al (2023)[13]	42 yo M	Bipolar affective disorder	VPA 1500 mg daily; risperidone 7 mg daily	7 days of VPA therapy	Not available	141 µg/dL
Vaidyanathan et al (2023)[13]	38 yo F	Bipolar affective disorder	VPA 1500 mg daily; risperidone 4 mg daily	After 19 years of VPA therapy	Not available	85 µg/dL

ADHD = attention-deficit/hyperactivity disorder; BID = two times a day; ER = extended release; F = female; M= male; TID = three times a day; VPA = valproate; yo = years old.

fraction of 10% at 40 mcg/mL and 18.5% at 130 mcg/mL.[17] Risperidone is 90% protein bound, whereas paliperidone is 77% bound.[18] Thus, it is plausible that paliperidone may also displace VPA in protein binding; however, the mechanism is not fully understood. The impact of other highly protein-bound drugs on the risk of VHE is unclear. Phenytoin, another highly protein-bound drug, is linked to cases of VHE, but the mechanism of this interaction may involve induction of VPA metabolism to toxic metabolites rather than displacement.[11] Alternatively, risperidone is recommended as a first-line combination treatment option for acute mania; thus, more patients may be prescribed this combination, potentially inflating the number of VHE cases seen.

In this case, the early symptoms of VHE were thought to be extrapyramidal symptoms (EPS). The patient exhibited excessive salivation and drooling, which was attributed to EPS causing a failure to swallow. The patient also displayed an unsteady gait, psychomotor retardation, and mild cogwheel rigidity, which are consistent with antipsychotic-induced parkinsonism. The incidence of EPS is more common than symptomatic VHE with an estimated prevalence of 20% (95% confidence interval 11% to 28%) of antipsychotic-induced parkinsonism among patients treated with antipsychotics.[19] In the presented case, VHE was considered when the patient displayed drowsiness and vomiting, prompting an ammonia concentration. Although VHE is less common than EPS in patients on this combination of medications, it should be considered in patients who display symptoms of altered consciousness or behavioral changes. These symptoms should prompt an immediate ammonia concentration regardless of VPA blood concentration or hepatic function. VHE in rare cases can manifest as a reversible Parkinson disease,[3] which may present similarly to antipsychotic-induced parkinsonism. It may be prudent to check an ammonia concentration in any patient cotreated with VPA and risperidone who presents symptoms of parkinsonism due to the potentially fatal nature of VHE and the growing evidence of a drug interaction between these two agents.

Conclusion

This report provides additional evidence of a drug interaction between risperidone and VPA that leads to an increased risk of VHE and suggests that the addition of paliperidone palmitate may increase this risk. More rigorous studies may be required to assess the full risk of VHE associated with this combination of medications. The extent of the risk seen with paliperidone and VPA is unknown and not reported in the literature, but as an active metabolite of risperidone, the potential for increased risk of VHE exists and is worth further investigation. This case report highlights the need for increased awareness of the interaction between risperidone and VPA and for prudent monitoring of patients prescribed this combination.

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