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Valproic Acid for Hyperactive Delirium and Agitation in Critically Ill Patients

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Abstract

Background: Delirium and agitation are common syndromes in critically ill patients. Valproic acid (VPA) has shown benefit in intensive care unit (ICU)-associated delirium and agitation, but further evaluation is needed.

Objective: The purpose of this study was to evaluate the effectiveness and safety of VPA for hyperactive delirium and agitation in critically ill adult patients.

Methods: A retrospective cohort study at NYU Langone Health was conducted in critically ill patients treated with VPA for hyperactive delirium or agitation from October 1, 2017 to October 1, 2022. The primary outcome was effectiveness of VPA, defined as a reduction in the total number of any concomitant psychoactive medication by day 3 of VPA treatment. Secondary outcomes included the effect of VPA on the doses of concomitant medications and adverse events.

Results: A total of 87 patients were included in the final analysis. By day 3 of VPA treatment, a 33% reduction ($P < .001$) in the total number of concomitant psychoactive medications was observed. VPA decreased the need for sedatives, as assessed by midazolam equivalents, but no significant changes were seen with dexmedetomidine alone, opioids, or antipsychotics. A 10 mg/kg loading dose was utilized in 36% of the cohort and its use decreased the risk for initiating additional psychoactive medications by day 3 of therapy (OR 2.8, 95% CI 1.0-7.8, $P = .047$), with benefits noted as early as 48 h after initiation. Adverse events were low in the total cohort (10.3%).

Conclusion and Relevance: The addition of VPA to a complex pharmacologic regimen for hyperactive delirium and agitation is safe and can assist in the prevention of polypharmacy and overall workload in critically ill patients admitted primarily for cardiogenic shock and respiratory failure requiring mechanical ventilation.

Keywords

delirium, agitation, valproic acid, sedatives

Introduction

Delirium and agitation are common psychiatric syndromes in critically ill patients, affecting up to 70% of those in the intensive care unit (ICU) and 82% of patients requiring mechanical ventilation.[1,2] Associated risk factors for delirium include benzodiazepine use, blood transfusions, increasing age, dementia, emergency surgery or trauma, and increasing Acute Physiology and Chronic Health Evaluation (APACHE) and American Society of Anesthesiology (ASA) scores.[3] The Society of Critical Care Medicine 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) in Adult Patients in the ICU recognize the need for a multimodal approach to managing delirium and agitation.[3] Specifically, haloperidol or atypical antipsychotics are not recommended for the prevention or treatment of

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delirium, unless patients experience extreme distress secondary to symptoms. Despite these recommendations, critically ill and agitated patients are often given antipsychotics for acute management.[3] Alternative pharmacotherapeutic options such as valproic acid (VPA) have shown potential benefit in ICU-associated delirium.[3]

Delirium is hypothesized to be mediated by a complex array of mechanisms including neuroinflammation, oxidative and physiologic stress, dysregulation in cellular signaling and secondary messenger systems, oxygen deprivation, cholinergic hypofunction, and neurotransmitter imbalance, including excess glutamate and dopamine and altered gamma-aminobutyric acid (GABA), serotonin, melatonin, and histamine levels.[4,5] VPA, an anticonvulsant medication and mood stabilizer, offers multiple mechanisms of action that can modulate biochemical pathways described with delirium, including attenuation of N-methyl-D-aspartate (NMDA) and modulation of GABA and dopaminergic pathways.[6,7] Appealing pharmacotherapeutic properties include its availability in both intravenous (IV) and oral (PO) formulations, hepatic metabolism allowing for use in critically ill patients with renal dysfunction, and minimal effect on QTc prolongation, especially compared to antipsychotics.[3,6] Additionally, VPA has not been shown to cause respiratory depression or increase the risk for delirium, as seen with benzodiazepines.[3] However, risk for drug-drug interactions with carbapenems and adverse effects, such as hepatotoxicity, thrombocytopenia, and hyperammonemia, all need to be considered before use.[8]

Given the limited data evaluating VPA for delirium and agitation in acutely agitated or critically ill adults, we aimed to evaluate prescribing patterns of VPA in the adult ICUs at a large academic medical center. We hypothesized that VPA would be effective at decreasing concomitant psychoactive medications including opioids, propofol, ketamine, benzodiazepines, dexmedetomidine, and antipsychotics, without an increase in serious adverse events.[9–17]

Methods

Study Population

This is a single center, retrospective, Institutional Review Board-approved, cohort study at NYU Langone Health (NYULH) of critically ill adult patients who were treated with $\geq$ 24 h of VPA for hyperactive delirium or agitation in any medical, surgical, or cardiac ICU from October 1, 2017 to October 1, 2022. Patients were included in the study cohort if they were $\geq$ 18 years of age, received at least one psychoactive medication for agitation or hyperactive delirium for $\geq$ 12 h prior to initiating VPA, and received VPA along with at least one other psychoactive medication for these indications for a minimum of 12 h in the ICU. Concomitant medications in this analysis included: continuous infusions of dexmedetomidine, propofol, ketamine, fentanyl, hydromorphone, and morphine; intermittent or continuous infusion benzodiazepines; antipsychotics, including haloperidol, olanzapine, quetiapine, risperidone, and any continued from home; clonidine; guanfacine; and gabapentin. Patents were excluded if they were located in the neurology or neurosurgical ICU, prescribed VPA prior to admission, treated with VPA for alternative indications (seizures, bipolar disorder, migraine, and alcohol withdrawal), or if the only concomitant psychoactive medication was a continuation of home antipsychotics or benzodiazepines at the same dose.

Data Collection

Electronic health records were reviewed to collect baseline demographics, including past neurologic and psychiatric history, risk factors for torsades de pointes (TdP) (any QTc greater than 500 milliseconds (ms) during the index hospital admission or a history of arrhythmia, coronary artery disease (CAD), or heart failure), psychoactive medications taken prior to admission (antipsychotics, benzodiazepines, opioids, antidepressants, and gabapentin), and baseline hepatic function and platelet levels. For up to 7 days of VPA treatment, additional information collected included VPA prescribing and monitoring practices, such as use of a loading dose, total daily dose [milligram (mg), mg/kilogram (kg)], route of administration, duration of therapy, therapeutic drug monitoring, and continuation of therapy at discharge. The incidence of any adverse event attributed to VPA, including hepatotoxicity, thrombocytopenia, pancreatitis, rash, and hyperammonemia was captured as well. To assess the study outcomes, the number of agents per day and the total daily dose of concomitant psychoactive medications were collected starting 24 h prior to and for up to 7 days of VPA treatment. Given the known propensity for carbapenems to reduce efficacy of VPA through increased clearance of the acylglucuronide form of VPA via inhibition of acylpeptide hydrolase, concomitant carbapenem usage during VPA treatment was collected.[18,19] All data collected were protected and kept confidential.

Outcomes

The primary outcome of this study was to assess the effectiveness of VPA in managing hyperactive delirium or agitation in critically ill patients. This was assessed by a percent change in the number of concomitant psychoactive medications, normalized per patient per day by day 3 after initiating VPA. The total number of agents, rather than individual components, was chosen given the retrospective design of the study. For any patient initiated on a carbapenem during the first 7 days of VPA treatment, the concomitant psychoactive medications were analyzed up until the day prior to the start of the carbapenem. Secondary outcomes included the effect of VPA on the doses of concomitant sedatives (dexmedetomidine, propofol, ketamine, benzodiazepines, continuous infusion opioids, and antipsychotics) by day 3 of VPA pharmacotherapy. Sedatives, opioids, and antipsychotics were assessed utilizing midazolam equivalents, fentanyl equivalents, and haloperidol equivalents, respectively (Supplemental Table 1). The effect on

dexmedetomidine alone was also assessed utilizing daily total dose in milligrams.[20–23] Patients requiring dexmedetomidine alone were separated from the midazolam equivalent analysis on the basis of decreased depth of sedation and differing pharmacology provided by dexmedetomidine.[24,25] Safety outcomes included hepatotoxicity, thrombocytopenia, hyperammonemia, pancreatitis, and rash. Hepatotoxicity was identified by an increase in aspartate aminotransferase (AST) > 3x the upper limit of normal (ULN), defined as 102 U/L, and/or alanine transaminase (ALT) > 3x the ULN, defined as 111 U/L, not attributable to an alternative etiology. Thrombocytopenia was defined by a decrease in platelets to less than 50 × 103/microliter (microL) and hyperammonemia by a new ammonia level > 60 micromol/liter (L) during VPA treatment. Pancreatitis and rash were identified upon chart review. Additionally, VPA prescribing practices and patient baseline demographics were assessed for any association with the primary outcome.

Statistics

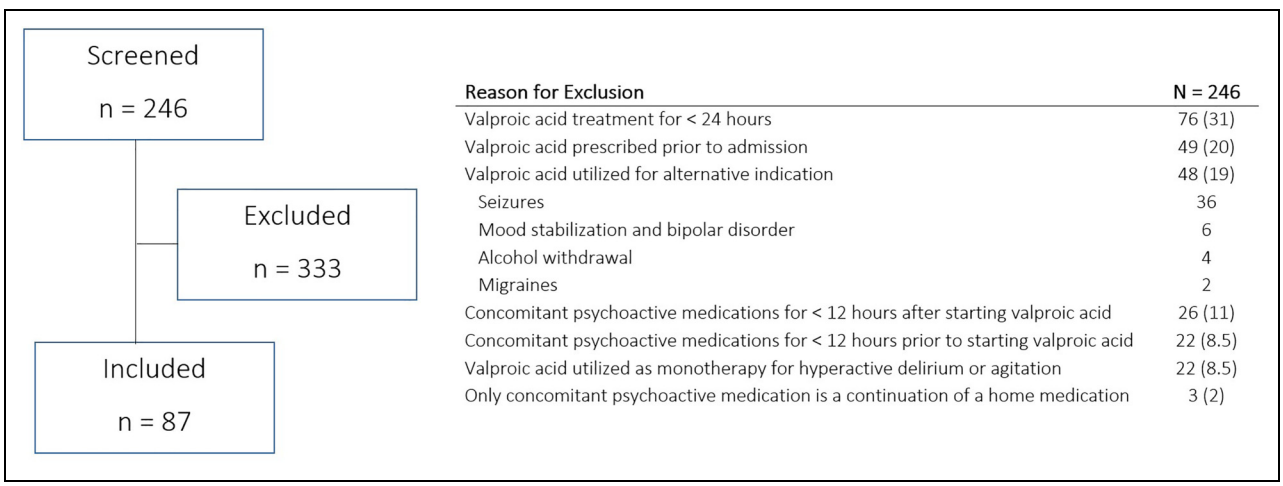
Continuous values were analyzed using Mann-Whitney *U* test for nonparametric data and reported as median with interquartile range (IQR), and categorical variables were compared using Chi-squared test or Fisher's exact test and reported as frequencies and proportion. Descriptive variables were reported as n (%), unless otherwise noted. The primary outcome was assessed by a percent change in the number of concomitant psychoactive medications, normalized per patient per day. To compare the effect of VPA over time, daily midazolam, fentanyl, and haloperidol equivalents were normalized for each patient to day 0 (baseline, the day prior to VPA initiation) and presented as a fraction of day 0 (Day N – day 0). Patients who received dexmedetomidine monotherapy were normalized for each patient to day 0 and presented as a fraction of day 0 (Day N – day 0). Daily normalized midazolam, fentanyl, and haloperidol requirements were presented as mean (standard deviation, SD). The patient's individual evaluation period was assessed while on VPA for up to 7 days, discontinuation of VPA, or initiation of a carbapenem, whichever came first. Linear mixed models were used in the analysis to account for repeated measures to account for missing cases throughout the evaluation period for daily midazolam, fentanyl, and haloperidol equivalents and dexmedetomidine total daily dose secondary to VPA discontinuation. With the maximum likelihood approach, we could use each patient's data for estimation of means for the 7-day evaluation period. Univariate analyses using odds ratio were performed on all collected variables to evaluate for characteristics associated with success of VPA administration by day 3 of treatment. *P* values < .05 were considered significant. All statistics were conducted using SPSS Statistics Software (IBM Corp., Armonk, NY; version 28.0).

Results

Study Population

A total of 333 patients were screened, with 87 included in the final analysis; reasons for exclusion are described in Figure 1. In the study cohort, 64% were male with a median (IQR) age of 64 years (54, 72), and SOFA score of 8 (5, 9). The primary indications for ICU admission included cardiogenic shock (38%) and respiratory failure (37%). A majority of the study population (68%) was mechanically ventilated for a median duration of 14 days (6, 29), 23% received mechanical circulatory support, and 10% required continuous renal replacement therapy (CRRT). Additional baseline characteristics, including past neurologic and psychiatric history, as well as pertinent baseline laboratory values and psychoactive medications prior to ICU admission, are included in Table 1. Hospital length of stay was a median of 31 days (19, 52) and ICU length of stay was 22 days (11, 37). Mortality occurred in 17% of the total population (n = 15).

Prior to admission, 36 patients (41%) were prescribed a psychoactive medication, with 15 (17%) receiving more than 1 agent (Table 1). Continuation of these home medications during the ICU admission were as follows: 11/36 (31%)



Reason for Exclusion	N = 246
Valproic acid treatment for < 24 hours	76 (31)
Valproic acid prescribed prior to admission	49 (20)
Valproic acid utilized for alternative indication	48 (19)
Seizures	36
Mood stabilization and bipolar disorder	6
Alcohol withdrawal	4
Migraines	2
Concomitant psychoactive medications for < 12 hours after starting valproic acid	26 (11)
Concomitant psychoactive medications for < 12 hours prior to starting valproic acid	22 (8.5)
Valproic acid utilized as monotherapy for hyperactive delirium or agitation	22 (8.5)
Only concomitant psychoactive medication is a continuation of a home medication	3 (2)

Figure 1. Enrollment and reasons for exclusion.

Table 1. Baseline Characteristics.

Demographics	N = 87
Age, years, median (IQR)^	64 (54, 72)
Male	56 (64)
Race/Ethnicity	
Caucasian	49 (56)
Black	20 (23)
Other	14 (16)
Asian	2 (2.5)
Asian Indian	2 (2.5)
Height, cm, median (IQR)	170 (163, 178)
Actual body weight, kg, median (IQR)	81.1 (68.1, 95.8)
Body mass index (BMI), kg/m^2, median (IQR)	28 (24, 32)
Serum creatinine (SCr), mg/dL, median (IQR)	1.1 (0.8, 2)
Requiring continuous renal replacement therapy (CRRT)	9 (10)
Indication for ICU admission	
Cardiogenic shock	33 (38)
Respiratory failure	32 (37)
Sepsis	16 (18)
Postoperative care	6 (7)
ICU Setting	
Cardiothoracic surgery	32 (37)
Medical	24 (28)
Surgical	22 (25)
Cardiac	9 (10)
Requiring mechanical ventilation	59 (68)
Duration of mechanical ventilation, days, median (IQR)	14 (6, 29)
Requiring mechanical circulatory support (MCS)	20 (23)
SOFA score, median (IQR)	8 (5, 9)
Past Medical History	
Any neurologic comorbidity	21 (24)
Stroke	16 (18)
Seizures or epilepsy	7 (8)
Traumatic brain injury	2 (3)
Any psychiatric comorbidity	28 (32)
Depression	15 (17)
Anxiety	9 (10)
Substance use disorder	9 (10)
Alcohol use disorder	6 (7)
Schizophrenia	1 (1)
Any risk factor for Torsades de Pointes	63 (72)
QTc > 500 ms from admission to VPA initiation	43 (49)
Heart failure	39 (45)
Coronary artery disease	29 (33)
Arrhythmias	27 (31)
Cirrhosis	1 (1)
Psychoactive Medications Prior to Admission	
Antidepressants	24 (48)
Gabapentin	13 (15)
Benzodiazepines	12 (14)
Opioids	7 (8)
Antipsychotics	4 (5)
Baseline Laboratory Values	
Aspartate aminotransferase (AST), U/L, median (IQR)	44 (25, 84)
Alanine transaminase (ALT), U/L, median (IQR)	28 (17, 55)
Alkaline phosphatase, U/L, median (IQR)	78 (59, 143)
Total bilirubin, mg/dL, median (IQR)	0.9 (0.6, 1.8)
Platelets (PLT), 10^3/microL, median (IQR)	130 (94, 197)
Albumin, g/dL, median (IQR)	2.8 (2.6, 3.1)

All values listed as n (%), unless otherwise indicated.
^IQR: interquartile range, SOFA: sequential organ failure assessment score.

received antidepressants, 7/36 (19%) received gabapentin, 4/36 (11%) received opioids, 3/36 (8%) received benzodiazepines, and 2/36 (6%) received their home antipsychotic regimen. Prior to initiation of VPA, 13/87 (15%) patients required 1 concomitant psychoactive medication, 18/87 (20%) required 2, 36/87 (40%) required 3, 13/87 (15%) required 4, and 7/87 (8%) required 5 or more medications. The median number of agents prior to VPA initiation was 3 (2, 3). Dexmedetomidine was the most common psychoactive medication utilized at baseline (n = 80, 92%). Over half of the patients (n = 46, 53%) were receiving opioids at baseline.

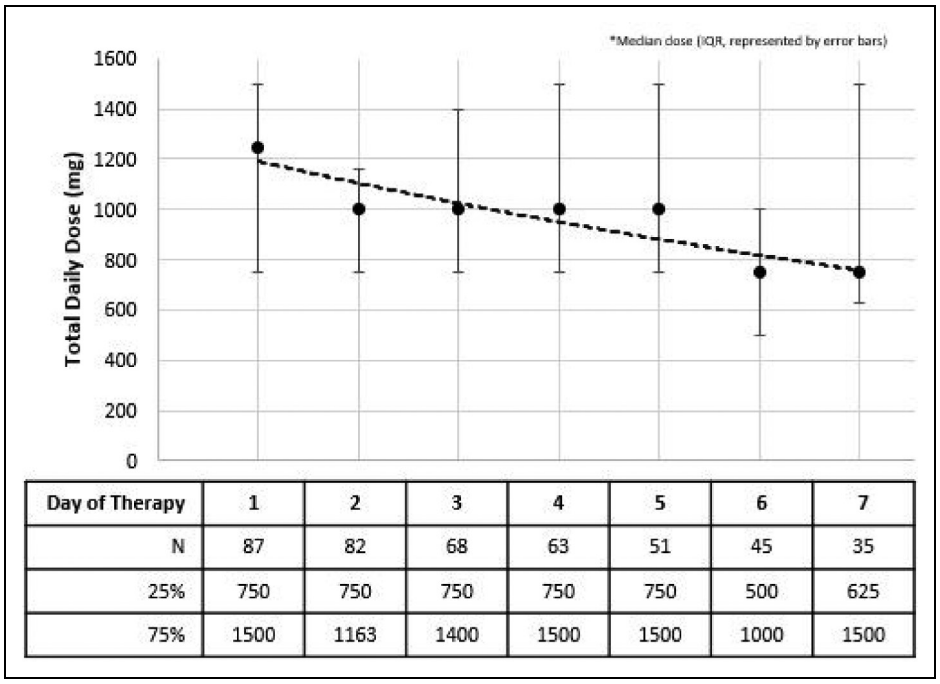
VPA for ICU Delirium

VPA was initiated at a median dose of 500 mg (250, 500), or 5.3 mg/kg. A loading dose was utilized in 31 patients (36%) at a median dose of 800 mg (500, 1000), or 10 mg/kg. The initial dose was given IV in 68 patients (78%) and was initiated 6.5 days (2.9, 15.8) into the ICU admission. The median duration of VPA was 6 days (4, 10). Of the total cohort, 68 (78%) and 35 (40%) patients remained on VPA by day 3 and day 7 of treatment, respectively. Figure 2 highlights the trend in the total daily dose of VPA over the 7 day treatment period. VPA was continued in 5 patients (6%) upon discharge.

Therapeutic drug monitoring of VPA was performed in 47 patients (54%), with a total of 97 levels and a median of 2 levels drawn per patient. The first VPA level was drawn after a median treatment duration of 3 days (2, 5). Of these levels, 49% (n = 48) were drawn at an appropriate trough time and the remainder were random levels. The median VPA level was 43 microgram/milliliter (mcg/mL) (27, 59) for all levels, but was 40 mcg/mL (26, 52) when assessing true troughs. The median albumin level at the time of the VPA level draw was 2.8 grams/deciliter (g/dL) (2.6, 3.1).

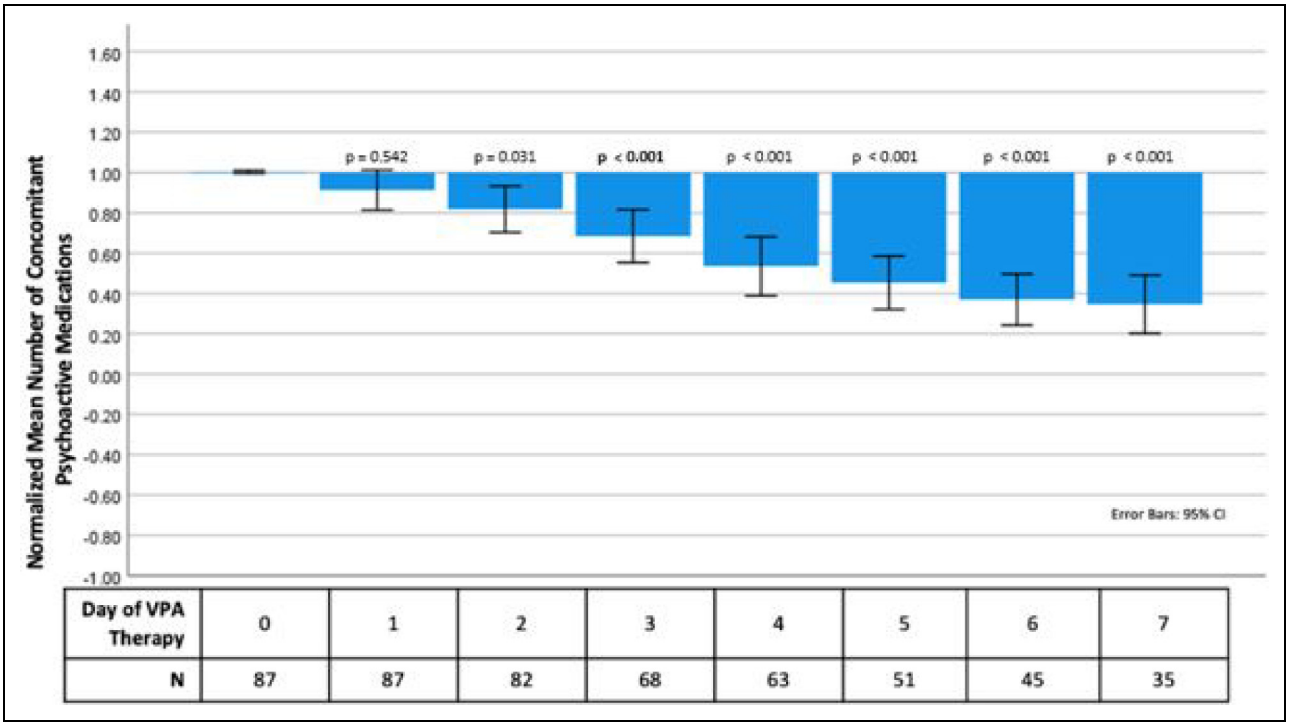
Primary Outcome

By day 3 of VPA treatment, a 33% reduction in the total number of any concomitant psychoactive medication was observed ($P < .001$) (Figure 3). This effect was seen as soon as day 2 of VPA therapy (18% reduction, $P = .031$) and continued for the total 7-day analysis period. Details on the total number of concomitant psychoactive medications per person per day are listed in Appendix A. For this analysis, 19 patients (22%) had missing data due to VPA discontinuation prior to day 3. Of these patients, 7/19 (37%) stopped VPA due to starting meropenem; 8/10 (42%) experienced a decrease in concomitant



Day of Therapy	1	2	3	4	5	6	7
N	87	82	68	63	51	45	35
25%	750	750	750	750	750	500	625
75%	1500	1163	1400	1500	1500	1000	1500

Figure 2. Valproic acid total daily dose per day.



Day of VPA Therapy	0	1	2	3	4	5	6	7
N	87	87	82	68	63	51	45	35

Figure 3. Primary outcome.

psychoactive medications, and 4/19 (21%) experienced an increase or no change in the number of concomitant psychoactive medications prior to stopping VPA. Numerically, for patients still receiving VPA by day 3 of therapy, the median reduction in concomitant medications in the overall cohort was 2 (1, 3).

Secondary Outcomes

An observed significant decrease in the total exposure of concomitant sedatives by day 3 of treatment, expressed as mean midazolam equivalents, was seen with VPA pharmacotherapy as early as day 1 of therapy (Figure 4), but no significant

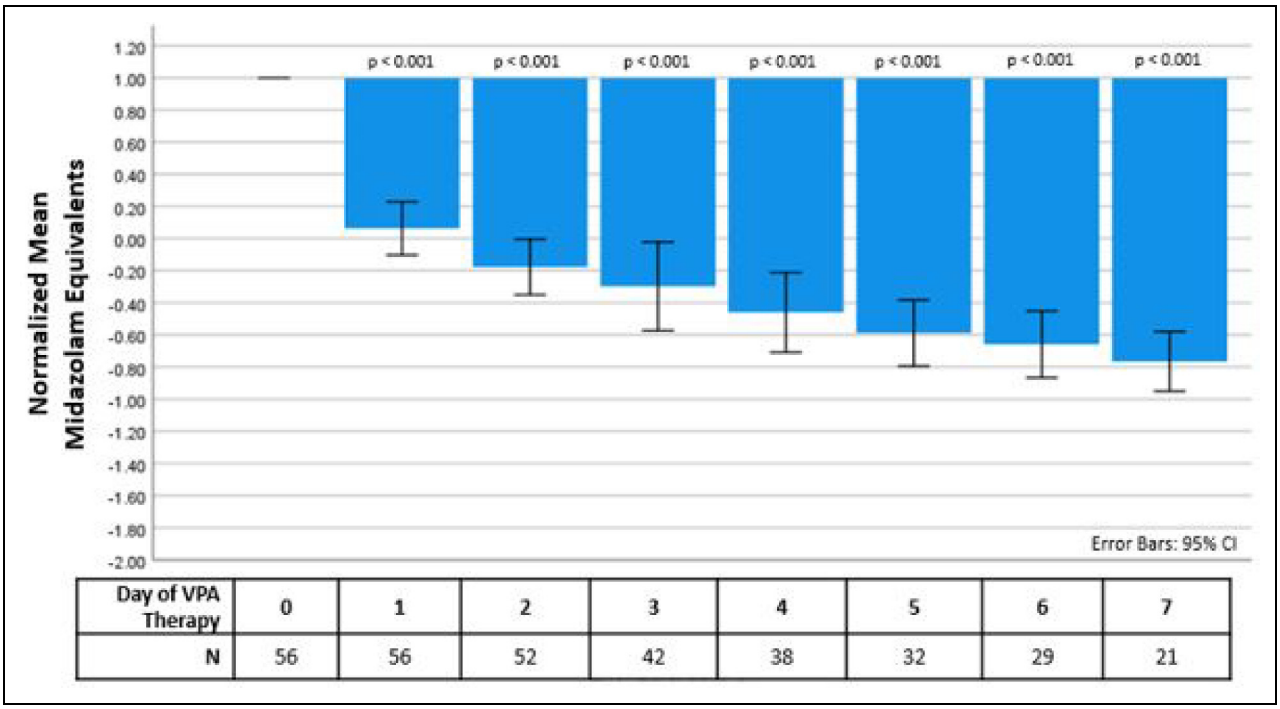


Figure 4. Effect of VPA therapy on concomitant sedatives.

changes were seen with dexmedetomidine alone, concomitant opioid infusions, or concomitant antipsychotic therapies.

A total of 9 patients (10.3%) experienced an adverse event. Hepatotoxicity, thrombocytopenia, and hyperammonemia occurred in 3.4% (n = 3) of the cohort each, with all events in unique patients. The incidence of hepatotoxicity was likely confounded by additional disease states encountered in critically ill patients, such as shock. Two patients had VPA discontinued secondary to elevation in hepatic enzymes. In all three patients with thrombocytopenia, the platelet level was low (61, 75, and 108 103/microL) at baseline, and may be confounded by characteristics of critical illness as well. The clinical significance of hyperammonemia in these patients is not clear, but no interventions were made secondary to this finding (62, 67, and 123 micromol/L). There was no incidence of pancreatitis or rash in this cohort.

Exploratory Outcomes

The univariate analysis evaluated for characteristics associated with success of VPA administration by day 3 of treatment. Patients were divided into two groups based on the mean number of concomitant psychoactive medications decreased by day 3: those who decreased by ≥ 2 agents (n = 25) and those who decreased by < 2 agents (n = 43). However, only patients still receiving VPA therapy were included in this analysis. For this analysis, 19 patients (22%) had missing data due to VPA discontinuation prior to day 3, as delineated above. For the remaining 68 patients (78%), the use of a loading dose was significantly associated with the primary outcome (OR 2.8, 95% confidence interval 1.0-7.8, $P = .047$). Numerically, by day 3 of therapy, patients who received a loading dose were receiving a median of 2 (1, 3) less agents compared to 1 (0, 2) less agent in all other patients. There was no significant association with the primary outcome when using IV versus PO therapy, if meropenem was administered within the 10 days prior to starting VPA, nor with mechanical ventilation.

Discussion

The use of VPA for the management of agitation and hyperactive delirium in the ICU has gained interest due to the perceived benefits of harm-avoidance of adverse events from other agents. However, data evaluating the optimal dosing, time of initiation, and overall safety of VPA for ICU delirium remains limited. In our study, VPA was initiated for ICU-associated delirium about one week into ICU admission at a median initial dose of 500 mg intravenously and total daily dose of 1000 mg/day for a duration of 6 days. This dosing strategy led to a 33% decrease in usage of concomitant psychoactive medications by day 3 of VPA treatment, with the effect seen as early as day 2 of therapy. These findings are consistent with another retrospective study of 47 critically ill patients, where a reduction in the proportion of patients requiring dexmedetomidine, benzodiazepines, antipsychotics, and opioids was found after 3 days of VPA, with dosing similar to our study.[12] An important finding from our analysis is that use of an initial loading dose at a median of 10 mg/kg was associated with a reduction in the total number of concomitant psychoactive medications by day 3 of VPA treatment, and thus reductions in polypharmacy.

Although there may be no statistical significance, patients who received a loading dose were on a numerically lower number of concomitant medications by day 3 compared to baseline (2 agents for those with a loading dose, 1 agent for those without), which is clinically significant. Notably, prior studies have reported VPA loading doses to range from 20–30 mg/kg, whereas our cohort had demonstrated success with use of lower doses.[13] Similarly, opioid, propofol, and haloperidol use was lower on day 3 of VPA therapy, with a resolution of delirium, but not agitation, in a cohort of 80 critically ill patients, when VPA was administered at a median dose of 750 mg/day without a loading dose.[14] Given the heterogeneous cohorts evaluated and variable dosing strategies and efficacy assessments of agitation/delirium by potentially subjective scoring tools, we aimed to assess the success of VPA by focusing on resource utilization. Although we did find a benefit in midazolam equivalent reduction over a 7-day period, we did not find a significant reduction in use of opioids, antipsychotics, or dexmedetomidine alone. Based on these results, we hypothesize that VPA may help reduce the required doses and overall number of GABA-ergic medications required to manage hyperactive delirium and agitation in critically ill patients. Providing a loading dose may achieve a faster steady state and time to response, given the prolonged half-life of 9–19 h. By reducing the total number of concomitant psychoactive medications required to manage these syndromes, ICUs may benefit from decreased resource utilization in terms of drug expenditure and nursing labor with monitoring and titration of continuous infusions of sedatives. In addition, the effect on polypharmacy and overall hospital care should be further investigated.

In general, the appealing pharmacologic properties of VPA, including the overall limited cardiovascular adverse effects, make it appealing for ICU-associated delirium, especially in cardiac intensive care units. Notably, the majority of our cohort had at least one risk factor for TdP (72%), with half the patients (49%) experiencing QTc prolongation >500 ms prior to VPA initiation, and 45% and 31% had a history of heart failure and arrhythmias, respectively, which may have influenced selection of this agent. However, VPA use may be limited in ICU patients with multi-drug resistant pathogens due to its drug-drug interaction with carbapenems; 7/87 (8%) of our total cohort had VPA therapy stopped due to addition of meropenem. Also, adverse events warrant cautious use, including hyperammonemia, thrombocytopenia, and hepatotoxicity, but the overall incidence of any of these in our cohort was 10.3%, consistent with previously reported data.[9–17] We believe that this rate is tolerable for a cohort of critically ill patients. Increases in hepatic enzymes and thrombocytopenia were the most common in our cohort, but the rate of each was low and likely confounded by critical illness. Though not insignificant, the rates of these are much lower than with antipsychotics, as seen in the Hope-ICU cohort of 71 critically ill patients, where high rates of QTc prolongation (n = 7, 10%) and arrhythmias such as atrial fibrillation (n = 7, 10%), supraventricular tachycardia (n = 4, 6%), and bradycardia (n = 2 3%) with haloperidol use were reported; these are less ideal for critically ill patients, especially those in cardiac ICUs.[26]

Therapeutic drug monitoring of VPA may be a way to assess overall safety and tolerability, although a specific value suggesting efficacy for agitation or delirium remains unknown. In our cohort, over half of the patients had at least one VPA level drawn, with a median value of 43 mcg/mL and concomitant albumin of 2.8 g/dL. Although we did not observe any dose changes or discontinuations due to these values, these levels are reassuring that the risk of toxicity with doses < 1000 mg/day appears low in critically ill patients. Consistent with our findings, VPA levels < 100 mcg/mL are associated with low incidence of adverse events. Multiple patient characteristics alter VPA pharmacokinetics and protein binding, causing discordance with measured total concentrations and the actual free concentration.[27–30] Lower serum albumin and increased total VPA levels have been associated with increased free VPA concentrations.[27] Hypoalbuminemia is common in hepatic and renal dysfunction, and critically ill patients as well.[28–30] Given that all patients in our cohort were in the ICU, with a median SCr of 1.1 mg/dL and 10% requiring CRRT, the total VPA concentrations obtained in our study may underestimate the effective VPA concentration, but remain reassuring for overall tolerability when used for agitation.

Limitations

There are several limitations to our study, including the single-center, observational, and retrospective design and potential for selection bias. In addition, we evaluated success of VPA by evaluating reduction in concomitant sedatives instead of effects on agitation or delirium, given inconsistent documentation of the Confusion Assessment Method for the ICU (CAM-ICU). However, the results observed in our study are similar to previous studies that did observe not only a benefit in the CAM-ICU score but also a reduction in other concomitant medications, adding to the growing literature supporting VPA use in this setting. In addition, we did not compare our results to a similar cohort of patients who did not receive VPA treatment, so it is possible patients improved with time and treatment of their underlying disease state(s) rather than secondary to the addition of VPA pharmacotherapy alone; reduction in concomitant benzodiazepines may have occurred over time as patients improved from their critical illness. In this retrospective study, we also could not delineate between hyperactive delirium and agitation. Additionally, we could not conduct specific subgroup analyses in patients who received only other agents known to improve delirium outcomes, namely dexmedetomidine and quetiapine, as it fell outside the scope of our review and would not yield conclusive results due to limitations imposed by a smaller sample size of heterogenous patients; it is possible these interventions could contribute to the reduction in use of concomitant sedative agents seen in our study. For our primary outcome, we acknowledge that 22% of the cohort were no longer receiving VPA by day 3 of therapy, and we addressed this by performing a linear mixed

model to account for immortal time bias and missing data points. For the univariate analyses, we recognize the potential use of relative risk, however, we included odds ratio in this retrospective review. Odds ratio, unlike relative risk, is not influenced by the patients' baseline risk or the outcome's prevalence within the patient population, therefore the odds ratio can represent the strength of the association of VPA to our outcome and can be a true measure of the effect magnitude. Further, our study had underrepresentation of patients with significant liver dysfunction and sepsis, and excluded those being treated for seizures, which may limit the generalizability of our results. In patients with severe liver dysfunction or hepatotoxicity, it may be wise to avoid use of VPA given its extensive reliance on hepatic metabolism; alternative agents with anti-deliriogenic effects, such as dexmedetomidine and quetiapine, could be considered, as appropriate. The manner in which septic patients were described within the baseline characteristics of this study may underrepresent the true prevalence (ie, many patients with respiratory failure as their primary indication for ICU admission likely have sepsis requiring treatment for pneumonia). Thus, the generalizability to patients with sepsis may still be limited, but can be considered. In critically ill patients with multiple risk factors for multi-drug resistant (MDR) gram negative organisms necessitating carbapenem treatment, the use of VPA may be limited and should be carefully considered by clinicians at the bedside.

Conclusion and Relevance

While helpful when managing behavioral changes seen with delirium, antipsychotics carry unique risks, including QTc prolongation, arrhythmias, and delirium itself. VPA may offer a unique opportunity for clinicians to assist patients with hyperactive delirium and agitation that avoids such harmful effects. Initiated with a 10 mg/kg loading dose, VPA may decrease polypharmacy as early as 48 h into therapy, with continued benefit for the duration of therapy, in critically ill patients with cardiogenic shock or respiratory failure requiring mechanical ventilation. Further studies with more robust definitions for delirium and agitation, including CAM-ICU and use of restraints, are needed to elucidate an optimal dosing strategy and the utility of therapeutic drug monitoring, as well as time to resolution of hyperactive delirium and agitation, with the addition of VPA.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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