Valproate for agitation in critically ill patients: A retrospective study

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A R T I C L E   I N F O

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A B S T R A C T

Purpose: The purpose was to describe the use of valproate therapy for agitation in critically ill patients, examine its safety, and describe its relationship with agitation and delirium.

Materials and methods: This retrospective cohort study evaluated critically ill adults treated with valproate for agitation from December 2012 through February 2015. Information on valproate prescribing practices and safety was collected. Incidence of agitation, delirium, and concomitant psychoactive medication use was compared between valproate day 1 and valproate day 3. Concomitant psychoactive medication use was analyzed using mixed models.

Results: Fifty-three patients were evaluated. The median day of valproate therapy initiation was ICU day 7, and it was continued for a median of 7 days. The median maintenance dose was 1500 mg/d (23 mg/kg/d). The incidence of agitation (96% vs 61%, \( P < .0001 \)) and delirium (68% vs 49%, \( P = .012 \)) significantly decreased by valproate day 3. Treatment with opioids (77% vs 65%, \( P = .02 \)) and dexmedetomidine (47% vs 24%, \( P = .004 \)) also decreased. In mixed models analyses, valproate therapy was associated with reduced fentanyl equivalents (\( -185 \mu g/d, P = .0003 \)) and lorazepam equivalents (\( -2.1 \mu g/d, P = .0004 \)). Hyperammonemia (19%) and thrombocytopenia (13%) were the most commonly observed adverse effects.

Conclusions: Valproate therapy was associated with a reduction in agitation, delirium, and concomitant psychoactive medication use within 48 hours of initiation.

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1. Introduction

Agitation occurs in up to 70% of critically ill patients and is a significant source of distress for patients, families, and providers [1]. Sedatives are administered to >50% of intensive care unit (ICU) patients to alleviate agitation [2]. Choice of sedative is complex and largely driven by patient context. No sedative has consistently been shown to be superior to the rest, and alternative agents are greatly needed [3].

Most ICU patients, especially those requiring mechanical ventilation, are treated with opioids, propofol, and/or benzodiazepines [2,4]. Use of these agents is limited by adverse effects (eg, hemodynamic derangement or respiratory depression) and need for a monitored environment for safe administration [5]. New therapies for treating agitation are rarely introduced into practice, with dexmedetomidine being the most recent in 1999. Consequently, providers have increasingly repurposed older pharmacologic agents as ICU sedatives (eg, clonidine, phenobarbital, and valproate) [6,7].

Valproate is an antiepileptic and mood stabilizer approved for treatment of seizures, manic episodes associated with bipolar disorder, and migraine prophylaxis [8]. Mechanistically, it blocks voltage-dependent sodium and calcium channels, increases \( \gamma \)-aminobutyric acid (GABA) synthesis, potentiates GABA activity at postsynaptic receptors, blocks GABA degradation, and attenuates the activity of glutamate upon N-methyl-D-aspartate receptors [9,10]. Recently, valproate has been administered to critically ill patients to treat agitation and delirium, but there are few published reports to support this practice [11–14]. Valproate is an emerging treatment for ICU agitation because it allows patients to interact with their caregivers; can be administered outside of the ICU; has both an intravenous (IV) and enteral formulation; has a low drug acquisition cost; and has not been associated with respiratory depression, hemodynamic derangements, or delirium.

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In this study, we sought to (1) describe the use of valproate for agitation in critically ill patients, (2) examine the safety of valproate therapy, and (3) describe the relationship between valproate therapy and agitation and delirium.

2. Material and methods

2.1. Study design

We conducted this retrospective cohort study of critically ill patients treated with valproate for agitation from December 2012 through February 2015 at Maine Medical Center (MMC) (Portland, ME) and Intermountain Medical Center (IMC) (Murray, UT). Both institutions are tertiary, university-affiliated medical centers, with 42 and 84 ICU beds, respectively. The protocol was approved by the Institutional Review Boards at both medical centers (MMC IRB #4583X and IMC IRB #1040472), and the need for patient consent was waived.

Patients were included in a convenience sample if they were ≥18 years of age and treated with valproate for ≥2 days while in the ICU. Patients were excluded if they were prescribed valproate prior to hospitalization, if they received multiple courses of valproate during their admission, or if it was initiated for other indications (e.g., seizures or migraines). Neither institution had a dosing or monitoring protocol for valproate therapy when used for the treatment of ICU agitation.

2.2. Demographics and patient characteristics

Patient demographic data included age, sex, race, weight, body mass index, history of psychiatric diagnosis, alcohol or substance abuse, reason for ICU admission, need for mechanical ventilation, and Acute Physiology and Chronic Health Evaluation (APACHE) III score within 24 hours of ICU admission. Clinical outcomes were descriptive and included hospital length of stay, ICU length of stay, and ICU mortality.

2.3. Valproate prescribing practices

Drug administration data were collected from the electronic Medication Administration Record at both centers. Valproate data included total daily dose, route of administration, duration of therapy, time from ICU admission to initiation, mechanical ventilation at the time of initiation, serum concentration monitoring, use of an initial loading dose, use of a taper to discontinue therapy, and whether or not valproate was continued at ICU and hospital discharge. Continuation at hospital discharge was characterized as either possibly inadvertent or intentional with rationale.

2.4. Efficacy outcomes

Efficacy data were collected starting 2 days before valproate initiation and continuing for 7 days or until discontinuation, whichever came first. The 7-day interval was selected to allow a reasonable time to observe efficacy or lack thereof.

The daily proportion of agitated patients was examined. Richmond Agitation-Sedation Scale (RASS) scores were assessed at IMC, and Sedation-Agitation Scale (SAS) scores were assessed at MMC. Assessments of sedation documented in the electronic medical record have recently been shown to be reliable when dichotomized to oversedated or not oversedated [15]. Because the recording of RASS and SAS scores was inconsistent in this study and sometimes contradicted what was documented in caregiver notes, an algorithm was used to improve the accuracy of assessments (Electronic Supplement Fig. 1). If RASS or SAS scores were available, their accuracy was confirmed by reviewing caregiver notes. If the 2 sources agreed, at least 1 RASS score ≥1 or SAS score ≥5 defined an agitation day. If the 2 sources disagreed or sedation scores were unavailable, patients were assigned an agitation day if key words signifying agitation were identified in caregiver notes [1].

The daily proportion of patients with delirium was also evaluated. The Confusion Assessment Method for the ICU (CAM-ICU) results were assessed at both institutions. Because the recording of CAM-ICU results was infrequent, a validated chart review method was used in conjunction (Electronic Supplement Fig. 2) [16]. The sensitivity and specificity of the chart review method are 64% and 85%, respectively. The sensitivity and specificity of the CAM-ICU screening for ICU delirium range between 47% and 100% and between 71% and 100%, respectively, suggesting that the chart review method is valid [17]. If CAM-ICU scores were recorded, their accuracy was confirmed by reviewing caregiver notes. If the 2 sources agreed, at least 1 positive CAM-ICU assessment defined a delirium day. If the 2 sources disagreed or scores were unavailable, a chart review was conducted, and patients were assigned a delirium day if the abstractor answered yes to the following question: Is there any evidence from the chart of delirium (i.e., delirium, mental status change, inattention, disorientation, hallucinations, inappropriate behavior, or other) [16]?

The need for concomitant psychoactive medications was also examined and included opioids, benzodiazepines, antipsychotics, clonidine, dexametomidine, phenobarbital, and propofol. The number of doses and total daily dose of each agent were recorded, except for propofol, dexametomidine, and ketamine, where mean hourly doses were recorded. Opioids were converted to fentanyl equivalents (100 μg IV fentanyl = 1.5 mg IV hydromorphone = 10 mg IV morphine = 20 mg oral oxycodone), and benzodiazepines were converted to lorazepam equivalents (1 mg IV lorazepam = 2 mg IV midazolam) [18,19].

2.5. Safety outcomes

Safety parameters were examined for the hospital duration of valproate therapy. Records were specifically reviewed for possible valproate-induced hepatotoxicity, hematologic toxicity, hyperammonemia, pancreatitis, and Stevens-Johnson syndrome. The number of patients who had valproate discontinued because of a suspected adverse event was also recorded. Only patients who had baseline laboratory values prior to valproate initiation were assessed for laboratory-based adverse effects.

Hepatotoxicity was defined as a new alanine aminotransferase >3 times the upper limit of normal (ULN) (>120 U/L), alkaline phosphatase >2 times the ULN (>234 U/L), total bilirubin >2 times the ULN (>2 mg/dL), or a doubling of the baseline value if it was already abnormal following valproate initiation [20]. Suspected cases of hepatotoxicity were further assessed using the validated Roussel Uclaf Causality Assessment Method (RUCAM) [21].

Hematologic toxicity was defined as a new leucocyte count <4200 cells/mm³, absolute neutrophil count <2400 cells/mm³, or platelet count <140 000 cells/mm³ or platelet drop by >50% if platelets were already <140 000 cells/mm³ following valproate initiation. Thresholds were set according to the lower limit of normal for the MMC laboratory [22,23].

Hyperammonemia was defined as a new serum ammonia level >60 μmol/L following valproate initiation. Suspected cases of hyperammonemia were further reviewed for treatment strategies. Pneumonia was defined as a new serum lipase level >3 times the ULN (>189 IU/L) in the presence of clinical symptoms. A diagnosis of Stevens-Johnson syndrome was assessed by reviewing caregiver notes.

2.6. Statistical analysis

Continuous variables were reported as median values with interquartile range (IQR) and were compared between valproate day 1 and valproate day 3 with the Wilcoxon rank-sum test. Categorical and binary variables were reported as frequencies and percentages
and were compared between valproate day 1 and valproate day 3 with McNemar test for paired proportions. Valproate day 1 (day of valproate initiation) was selected as the baseline because it had the highest incidence of agitation, representing maximum agitation and the decision to prescribe valproate. Valproate day 3 was chosen for comparison based on the premise that failure to respond in 2 days would lead to a change in therapy. Analyses were conducted using Analyze-it v2.25, and $P < .05$ was considered statistically significant.

Repeated-measures models were used to assess concomitant psychotropic medication use over time. Linear mixed models were developed using a between-within degrees-of-freedom method, identifying subjects as repeated effects. Fixed effects were related to day of treatment, and a Toeplitz-structured covariance matrix was selected from a range of alternatives by minimization of the Akaike information criterion. The structure was fit to the data via the restricted maximum likelihood method, similarly selected to minimize the fit statistics. To avoid inappropriate deflation of the mean, each medication was assessed for response only for patients who actually received that agent. Linear models were obtained for each agent, estimating a slope and intercept relating day of treatment to daily dose. Analyses were conducted using SAS version 9.3, and $P < .05$ was considered statistically significant.

## 3. Results

### 3.1. Demographics and patient characteristics

Three-hundred fifty-one adult patients were treated with valproate during the study period. Two-hundred ninety-eight were excluded, leaving 53 evaluable patients representing 522 patient-days of valproate therapy (Fig. 1). The median (IQR) patient age was 53 (40-70) years, and most patients were male (64%) (Table 1). Respiratory failure (26%), trauma (22%), and acute stroke (15%) were the most common reasons for ICU admission. The median APACHE III score was 59 (40-73). The median ICU and hospital lengths of stay were 14 (9-20) and 22 (13-30) days, respectively. Seven (13%) patients died in the ICU, and 9 (17%) died in the hospital.

### 3.2. Valproate prescribing practices

The median time from ICU admission to valproate initiation was 7 (4-10) days (Table 2). Loading doses were administered to 22 (42%) patients at a median dose of 1800 (1500-2000) mg or 28 (19-31) mg/kg. The median maintenance dose on valproate day 3 was 1500 (1000-2275) mg/d or 23 (15-31) mg/kg/d administered in 1 to 4 divided doses. Valproate was tapered in 14 (26%) patients over a median of 3 (2-7) days by reducing the dose and/or increasing the dosing interval. Eighteen valproate total serum concentrations were obtained ($n = 9$ trough, $n = 8$ random, $n = 1$ unclear) in 8 (15%) patients and were a median of 49 (34-63) mg/L. Seventeen (32%) patients were continued on valproate at hospital discharge; 3 (18%) patients did not have clear rationale.

### 3.3. Efficacy outcomes

The incidence of agitation increased from 73% on valproate day −2 to 80% on valproate day −1 and to 96% on valproate day 1 (Fig. 2). The incidence of agitation significantly decreased following the initiation of valproate to 61% on valproate day 3 ($P < .0001$). The incidence of delirium exhibited a similar trend, occurring in 41% of patients on valproate day −2, 51% on valproate day −1, and 68% on valproate day 1 (Fig. 2). The incidence of delirium also decreased by valproate day 3 (48%, $P = .012$). The source of agitation and delirium assessments (SAS/RASS or CAM-ICU vs chart review) is described in Electronic Supplement Table 1. The impact of a loading dose on the incidence of agitation and delirium was also assessed, but statistical testing was not conducted because of the small number of patients in each group (Electronic Supplement Table 2).
The proportion of patients receiving an opioid decreased from valproate day 1 to valproate day 3 (77% vs 65%, \( P = .02 \)) (Table 3). Median daily fentanyl equivalents administered also decreased (1347 vs 800 \( \mu g/d, P = .04 \)). The number of patients receiving dexmedetomidine (47% vs 24%, \( P = .004 \)) and quetiapine (49% vs 35%, \( P = .04 \)) decreased by valproate day 3. Neither the number of patients receiving a benzodiazepine (53% vs 47%, \( P = .2 \)) nor the median lorazepam equivalents administered (10.5 vs 10 mg/d, \( P = .7 \)) were reduced. The impact of a loading dose on concomitant psychoactive medication use was also examined (Electronic Supplement Table 3). Fentanyl equivalents and lorazepam equivalents paradoxically increased in the loading dose subgroup, which might have been due to 3 patients who had excessively high sedative requirements.

Mixed models were created to assess the impact of valproate on daily concomitant psychoactive medication use (Electronic Supplement Figs. 3A-E). Fentanyl equivalents (\(-185 \mu g/d, P = .0003\)), lorazepam equivalents (\(-2.1 \text{mg/d, } P = .0004\)), dexmedetomidine dose (\(-0.15 \text{mg/kg per hour per day, } P < .0001\)), and propofol dose (\(-5 \text{mg/kg per minute per day, } P = .003\)) decreased, whereas quetiapine (\(-1 \text{mg/d, } P = .9\)) and clonidine (\(-0.02 \text{mg/d, } P = 8\)) dose did not. There were too few observations to create models for the remaining concomitant medications. Between-centers comparisons were not performed because of the small number of patients studied.

### 3.4. Safety outcomes

Most patients (79%) had liver function tests monitored before and during valproate therapy (Table 4). One patient developed an isolated elevated alkaline phosphatase (249 U/mL), with a RUCAM score of 4, suggesting a possible association with valproate. One patient had an elevated total bilirubin (2.4 mg/dL), but the RUCAM score was 1, suggesting that it was unlikely related to valproate. Valproate was not discontinued in either case.

All patients had a complete blood count obtained before and during valproate therapy (Table 4). Thrombocytopenia was the most common potential hematologic toxicity observed, occurring in 7 (13%) patients, with 1 having valproate discontinued. Two (5%) patients developed neutropenia, but neither had valproate discontinued.

Thirty-two (60%) patients had an ammonia level measured during valproate therapy (Table 4). Six (19%) patients had an elevated ammonia level >60 \( \mu mol/L \). Valproate was discontinued in 4 of these patients. No relationship between dose and hyperammonemia was observed (data not shown).

### 4. Discussion

Our study provides the most comprehensive information to date on valproate prescribing practices for ICU agitation. In addition, we describe the safety and efficacy of valproate therapy in greater detail than prior studies and more than double the number of reported patients treated with valproate for ICU agitation. In our study, valproate was initiated 1 week after ICU admission to treat escalating agitation. Loading doses were administered to 42% of patients, and the maintenance dose was 1500 mg/d (23 mg/kg/d) administered in 1 to 4 divided doses. This therapy was associated with a reduction in the incidence of agitation and delirium within 48 hours of initiation and a reduction in daily fentanyl and lorazepam equivalents administered in mixed models analyses. Observed adverse effects were infrequent, with thrombocytopenia and hyperammonemia being the most common.
We are aware of only 4 published reports of valproate to treat ICU agitation or delirium. A case series of 6 patients reported behavioral improvement with the addition of valproate (500-2500 mg in 2-4 divided daily doses) to more conventional treatments [11]. A second case series of 15 patients with hyperactive delirium demonstrated that valproate therapy (1133-1258 mg in 2-3 divided daily doses) resulted in delirium resolution in 13 of 16 episodes within 6.2 days [12]. A third case series of 2 patients with agitation and delirium reported that valproate therapy (500 mg in 2 divided daily doses) resulted in reduced agitation within 24 hours [13]. Lastly, an abstract-only publication reported that delirium resolution occurred by day 7 in 18 patients receiving valproate [14]. These reports provided important data but are limited by small sample sizes and limited descriptions of valproate prescribing patterns, safety, and efficacy.

Our study complements these reports in several ways. We collected detailed information on valproate prescribing practices. Valproate therapy was initiated a median of 1 week after ICU admission, which suggests that it was used in patients who were refractory to or intolerant of more traditional agents. Loading doses were used in 42% of our patients. Loading doses may achieve therapeutic serum concentrations more rapidly, but this practice has not been previously described for ICU agitation. Daily maintenance doses were slightly higher than those previously reported [11-13]. The optimal dosing regimen for valproate in the ICU—and whether loading doses are beneficial—is not answered by our research and should be addressed in future studies.

Valproate therapy was continued for a median of 7 days, and 43% of patients were transferred out of the ICU on it, which suggests that many patients were responding favorably and providers were comfortable transitioning patients to a non-ICU environment on this agent. On the other hand, it is possible that valproate was inadvertently continued upon ICU discharge. Seventeen patients (32%) were discharged from the hospital on valproate, which is consistent with published reports on the rate of continuation of psychoactive medications upon hospital discharge [6,24,25]. Strategies to prevent inadvertent psychoactive medication continuation are needed and are under way at our medical centers.

Within 48 hours of initiating valproate, the incidence of agitation and delirium decreased by 36% and 28%, respectively, relative to valproate day 1. Although we did not assess for the resolution of agitation and delirium, we found that symptom control occurred more quickly in our study than others, perhaps a function of slightly higher daily maintenance doses [12-14]. The anxiolytic effects of valproate

### Table 3

<table>
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<th>Medication</th>
<th>Valproate day −1</th>
<th>Valproate day 1</th>
<th>Valproate day 2</th>
<th>Valproate day 3</th>
<th>Valproate day 4</th>
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<tr>
<td>Opioid, n (%)</td>
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<td>41 (77)</td>
<td>41 (77)</td>
<td>33 (65)*</td>
<td>30 (64)</td>
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<tr>
<td>Fentanyl equivalents, μg/d</td>
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<td>1347</td>
<td>629</td>
<td>800*</td>
<td>467</td>
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<tr>
<td>Benzodiazepine, n (%)</td>
<td>31 (61)</td>
<td>28 (53)</td>
<td>25 (47)</td>
<td>24 (47)</td>
<td>24 (51)</td>
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<tr>
<td>Lorazepam equivalents, mg/d</td>
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<td>10</td>
<td>4</td>
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<tr>
<td>Dexametomidine, μg/kg/h</td>
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<td>25 (47)</td>
<td>19 (36)</td>
<td>12 (24)**</td>
<td>12 (26)</td>
</tr>
<tr>
<td>Quetiapine, mg/d</td>
<td>21 (41)</td>
<td>26 (49)</td>
<td>21 (40)</td>
<td>18 (35)*</td>
<td>17 (36)</td>
</tr>
<tr>
<td>Haloperidol, n (%)</td>
<td>10 (20)</td>
<td>9 (17)</td>
<td>8 (15)</td>
<td>9 (18)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Haloperidol, μg/kg/min</td>
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<td>10 (19)</td>
<td>9 (17)</td>
<td>9 (17)</td>
<td>9 (19)</td>
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<tr>
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<tr>
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<td>10</td>
</tr>
<tr>
<td>Quetiapine, mg/d</td>
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<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Haloperidol, mg/d</td>
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<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
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<td>2 (4)</td>
<td>3 (6)</td>
<td>6 (13)</td>
</tr>
</tbody>
</table>

Continuous variables reported as median (IQR) and categorical or binary variables as frequency (%). *P < 0.05 and **P < 0.01 for comparisons between valproate day 1 and valproate day 3.

* One patient received ketamine on valproate days 2 to 5 at a rate of 0.16 to 0.2 mg/kg/h.
might be due to GABA modulation or antagonism of glutamate at N-methyl-D-aspartate receptors [9,10]. Valproate is a potential option for the management of ICU delirium due to its proposed biochemical, anti-inflammatory, antioxidant, and transcriptional/neurotrophic effects [26]. A randomized controlled trial to assess valproate therapy for hyperactive or mixed ICU delirium is currently under way (NCT02343575).

Valproate has been used to treat agitation in other patient populations with mixed results. It has been used to treat behavior disorders in patients recovering from traumatic brain injury, but the overall quality of data is low [27,28]. Valproate has been associated with a trend toward increased mortality when used for seizure prophylaxis following traumatic brain injury (13.4% in the valproate group vs 7.2% in the phenytoin group; P = .07; relative risk, 2.0; 95% confidence interval, 0.9-4.1) [29]. This finding must be interpreted with caution because the study was not powered to assess mortality, the mortality rate in both groups was lower than the rate observed in a previous study in the same patient population at the same medical center, and the observation has not been confirmed in subsequent studies. A reassuring case-control study of more than 90,000 patients with dementia, a patient population that may be more similar to ours, found that valproate was not associated with mortality [30]. A systematic review and meta-analysis of valproate to treat agitation in dementia found that there were limited data to support that practice [31]. These findings have been corroborated by a more recent evidence summary published by the National Institute for Health and Care Excellence [32]. It should be emphasized that data describing valproate use in these patient populations cannot be generalized to ICU patients.

Hyperammonemia was the most common possible adverse effect observed, occurring in 15% of patients who had an ammonia level evaluated. Hyperammonemia, which may occur in 6% to 58% of valproate-treated patients, might be due to urea cycle interference by valproate and its reactive metabolite, valproyl-CoA [33,34]. A consistent correlation between hyperammonemia and valproate dose, serum concentration, or duration of therapy has yet to be described, and no such relationship was identified in our study [35]. In addition, ammonia levels may not correlate with the level of encephalopathy and are often elevated in patients without encephalopathy [35].

Thrombocytopenia was the most common possible hematologic adverse effect observed, occurring in 13% of patients. Only 1 patient had a platelet count decrease of >50% following valproate initiation. Thrombocytopenia may occur in 5% to 60% of valproate-treated patients and in 5% to 28% of valproate-treated psychiatric inpatients [36-39]. Valproate-induced thrombocytopenia may be due to dose-dependent bone marrow suppression and/or autoantibody formation [36]. We did not evaluate for valproate-associated disorders of hemostasis, but thrombocytopenia, hypofibrinogenemia, acquired von Willebrand disease type 1, and clotting factor deficiencies have been described [36]. Thrombocytopenia and coagulopathy are common in critically ill patients, and etiologies were difficult to assess given the retrospective nature of our study [40].

Total serum valproate concentrations were measured in 15% of patients, but no consistent approach to therapeutic drug monitoring was evident, as half of serum concentrations were trough determinations and half were randomly obtained. A total valproate serum concentration of 30 to 125 mg/L is recommended by the American Psychiatric Association’s guidelines for the treatment of patients with bipolar disorder, but this reference range has not been validated for ICU agitation [41]. Because valproate is highly protein bound to albumin (≥90%), its free fraction can vary as a function of altered plasma protein binding, which is common in critically ill patients [42]. Future research should attempt to correlate clinical effect and toxicity with free and total serum valproate concentrations [43].

Our study has limitations that warrant discussion. The small number of patients evaluated means that we were unable to confidently quantify adverse effects or estimate event rates. The retrospective design did not allow for direct patient observations; SAS or RASS scores and CAM-ICU results were sometimes unavailable. Our chart review method made up for some of this shortcoming, but prospective and routine evaluations of agitation and delirium would improve the reliability of our results. Other retrospective studies of ICU agitation and delirium have used a chart review similar to ours [44-46]. In addition, agitation is a continuum from mild restlessness to dangerous agitation; in this retrospective study, we could not define the severity of agitation that should trigger valproate therapy, but future prospective studies should address this issue. Because of these limitations, the effectiveness of valproate for both agitation and delirium in our study must be considered hypothesis generating and interpreted within the context of our methodology. The etiology of agitation was not defined, and we cannot recommend valproate therapy for a specific ICU patient population. Several patients had a history of a psychiatric diagnosis at baseline, but this was expected, as it has been associated with up to a 5-fold increase in the risk of ICU agitation [45,47]. Although our mixed models analyses reduced the bias from repeated measures, our sample size precluded their use in infrequently used medications. Practice variations between centers were not controlled and could have confounded our results. Lack of a control group prevented us from concluding that valproate was responsible for the behavioral improvement and not the result of critical illness resolution. Adverse effect monitoring was not standardized and could be underrepresented. Because of these limitations, our findings must be interpreted with caution and require confirmatory testing.

5. Conclusions

Valproate therapy is an emerging treatment option for ICU agitation not responding to more traditional pharmacologic agents. In our study, valproate therapy at a dose of 23 mg/kg/d was associated with a
reduction in agitation, delirium, and concomitant psychoactive medication use within 48 hours of initiation. Observed adverse effects were infrequent; providers should regularly monitor complete blood counts, liver function test results, and ammonia levels during valproate therapy. These promising results should be validated in prospective controlled studies.

**Conflicts of interest**

None.

**Financial disclosure**

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**Prior presentation of data**

Preliminary data were presented at the Society of Critical Care Medicine 45th Annual Critical Care Congress; February 20-24, 2016; Orlando, FL.

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jcrc.2016.09.006.

**References**


