Assessment of compliance to the recommended dosing for fosphenytoin, valproate, or levetiracetam in patients with benzodiazepine-refractory status epilepticus (BRSE)

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Introduction

- Each year, 50,000 to 150,000 Americans experience status epilepticus (SE). The seizure activity associated mortality is estimated to be 30% in adults.[1]
  - Progression to refractory SE and super refractory SE showed poorer prognosis and increased morbidity and mortality.[2]
  - Rapid termination of seizure activity with initial benzodiazepine therapy and second phase antiepileptic drugs (AED) is crucial by using the evidence-based recommended dose.
- The American Epilepsy Society (AES) guideline included the optimal doses of each agent for patients with SE lasting more than 20 minutes when initial benzodiazepine therapy failed.[3]
  - IV fosphenytoin 20 mg PE/kg at max 1500 mg PE/dose
  - IV valproic acid 40 mg/kg at max 3000 mg/dose
  - IV levetiracetam 60 mg/kg at max 4500 mg/dose
- Parsons A, et al. reviewed AED dosing compliance to the AES guideline and found significant suboptimal dosing of AEDs[4]
  - IV fosphenytoin 17.9 mg/kg (n=47)
  - IV valproic acid 16.7 mg/kg (n=12)
  - IV levetiracetam 21.7 mg/kg (n=42)

Purpose

The purpose of this study is to evaluate compliance to the recommended dosing for fosphenytoin, levetiracetam, and valproic acid based on the AES guideline in patients with BRSE. This evaluation is anticipated to offer a retrospective observation of the facility's adherence to the evidence-based guideline for status epilepticus treatment.

Methods

Design: Single center, medication use evaluation of 64 adult patients admitted to the emergency department (ED) from Jan 2016 to June 2020
Inclusion Criteria: Nonpregnant, adult patients aged between 18 and 85 years old, ICD-10 diagnosis of SE and/or provider's note included diagnosis of SE, and use of one AED including fosphenytoin, valproic acid, or levetiracetam
Exclusion Criteria: Other AED use, missing data
Data Collected: Demographics (age, gender, weight, admission year, diagnosis of SE), choice of AED with its respective dose (mg/kg), choice of benzodiazepine with cumulative dose during initial therapy, and purpose of AED use (either prophylaxis of further seizure activity or BRSE)

- Multiple AED use: First drug only accounted for in terms of the primary outcome
- Benzodiazepine cumulative dosing expressed as lorazepam equivalents

Primary Endpoint: Average dose of AED used in patients with SE
Secondary Endpoint: Average dose of benzodiazepine in patients with SE
Statistical Analysis: Mean, median, and mode dose of each drug based on the patient's body weight (mg/kg) and percentage of compliance to the AES guideline in terms of AED dosing

Results

Figure 1: Screening Process

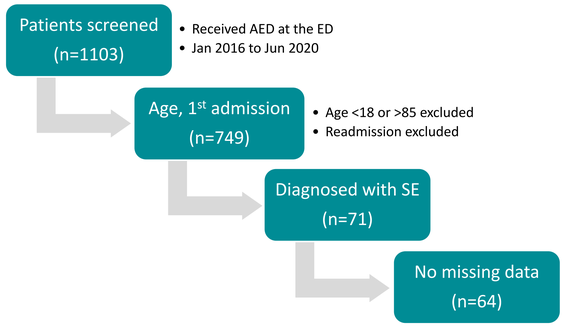


Table 1: Baseline characteristics

Characteristics	N=64	Range
Mean age	53	18 – 79
Female (%)	30 (47%)	
Mean Weight (kg)	79.5	40 – 139
Admission year		
2016	13	
2017	9	
2018	14	-
2019	22	
2020 (By June)	6	
Use of AED		
Prophylaxis for further SE*	23	
BRSE	25	-
Not known§	7	
Not documented	9	
Choice of AED		
Fosphenytoin (%)	18 (28%)	
Valproic acid (%)	4 (6%)	-
Levetiracetam (%)	42 (66%)	
Choice of benzodiazepine		
Lorazepam (%)	37 (58%)	
Midazolam (%)	22 (34%)	-
Diazepam (%)	1 (1%)	
Not given (%)	4 (7%)	
Benzodiazepine dose repeated		
Yes (%)	45 (75%)	-

** Patients responded to initial benzodiazepine therapy, but AED was prescribed for prophylaxis of further seizure activity.*
§ Patients who were immediately intubated with or without initial benzodiazepine therapy and unable to determine true BRSE

Table 2: Mean, median, and mode dose of each AED

Dose	Fosphenytoin (mg/kg)	Valproic acid (mg/kg)	Levetiracetam (mg/kg)
Mean	17.5 ± 2.48	17.3 ± 4.79	19.7 ± 10.99
Median	18	18.5	17
Mode	20	21	11

Figure 2: Use of AED trend per year

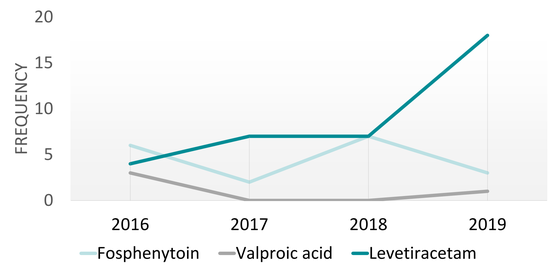


Figure 3: AES guideline compliance (n=64)

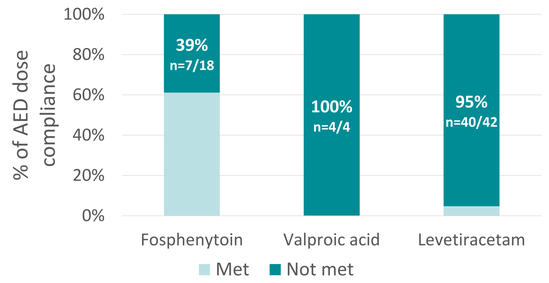


Figure 4: AES guideline compliance in subgroup of patients with true BRSE, who did not respond to initial benzodiazepine therapy (n=25)

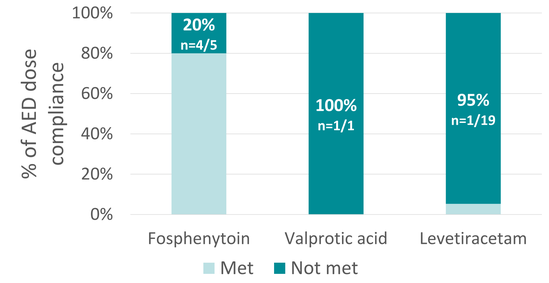
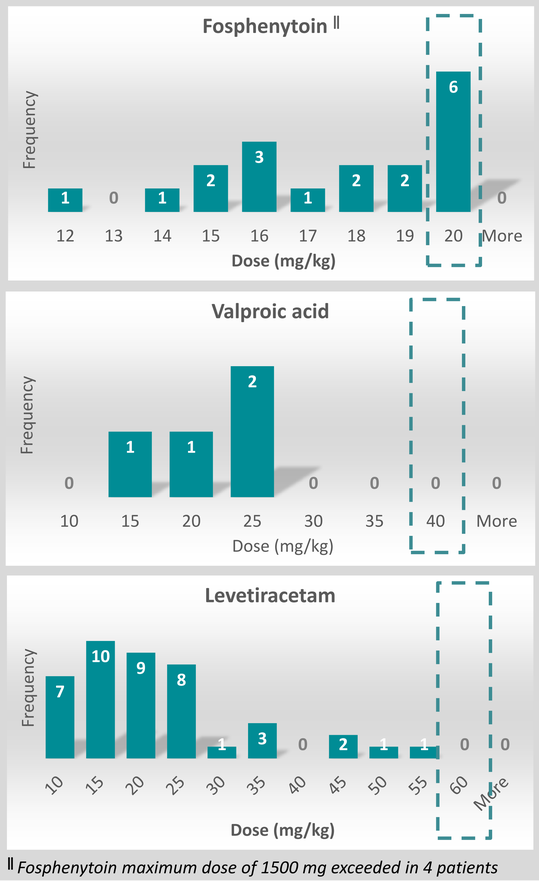


Figure 5. Fosphenytoin, valproic acid, and levetiracetam's dosing regimen frequency. The box represents AES recommended dosing.



‖ *Fosphenytoin maximum dose of 1500 mg exceeded in 4 patients*

Hypothesis

- **Hypothesis 1: The underdosing of AEDs is due to lack of confidence in clinical diagnosis of BRSE**
  - 64 patients diagnosed with SE received one AED in the ED, but significant suboptimal dosing of AEDs resulted, especially in levetiracetam.
  - The percentage of AES guideline compliance was 5% in levetiracetam. Unlike the guideline's recommended with dosing of 60 mg/kg (max dose 4500 mg), the average dose of levetiracetam was 19.7 mg/kg.
  - Most patients received levetiracetam 1000 mg IV in the ED despite SE diagnosis, which was not considered to be a weight-based dose.
  - Levetiracetam underdosing was identically observed in the subgroup of true BRSE patients as shown in figure 4.
- **Hypothesis 2: The underdosing of AEDs is due to the fear of adverse effects by using the aggressive dose of AEDs.**
  - In 2019, use of levetiracetam significantly outweighed the use of fosphenytoin and valproic acid.
  - Among the three AEDs, fosphenytoin has had the highest compliance rate to the AES guideline as its maximum dose for BRSE is considered to be low of 1500 mg at a glance compared to the maximum dose of levetiracetam which is 4500 mg.
- **Hypothesis 3: Underdosing of AEDs would be even more prominent in the future.**
  - Fosphenytoin utilization is decreasing while levetiracetam's utilization is increasing for BRSE. If fosphenytoin was excluded, underdosing of AEDs would be even more prominent in the future based on this data.

Conclusion

Patients who were diagnosed with SE received suboptimal doses of both initial benzodiazepines and AEDs in the ED. Study results were shared with Atrium Health Cabarrus ED pharmacists and ED physician education was provided which can help guide optimal AED dosing.

References

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Disclosures

Authors of this presentation have the following to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation. Sebin Yang, PharmD nothing to disclose; Robert Wozniak, PharmD, BCPS, BCCCP nothing to disclose.