MR. ABHISHEK G SATHE (Orcid ID : 0000-0002-7348-4208)

DR. HANNAH R. COCK (Orcid ID : 0000-0002-5656-0141)

DR. THOMAS P. BLECK (Orcid ID : 0000-0002-8267-9787)

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Title: The Association of Patient Weight and Dose of Fosphenytoin, Levetiracetam and Valproic acid with Treatment Success in Status Epilepticus

Authors List: Abhishek G. Sathe[1]; Jordan J. Elm[2]; James C. Cloyd[1]; James M. Chamberlain[3]; Robert Silbergleit[4]; Jaideep Kapur[5,6]; Hannah R. Cock[7]; Nathan B. Fountain[5]; Shlomo Shinnar[8]; Daniel H. Lowenstein[9]; Robin A. Conwit[10]; Thomas P. Bleck[11] and Lisa D. Coles[1]

Author Affiliations: [1]Department of Experimental and Clinical Pharmacology and Center for Orphan Drug Research, College of Pharmacy, University of Minnesota, Minneapolis, MN; [2]Department of Public Health Science, Medical University of South Carolina, Charleston, SC; [3]Division of Emergency Medicine, Children's National Hospital and the Department of Pediatrics and Emergency Medicine, School of Medicine and Health Sciences, George Washington University Washington, DC; [4]Department of Emergency Medicine, University of Michigan, Ann Arbor, MI; [5]Department of Neurology and [6]Department of Neuroscience, Brain Institute, University of Virginia, Charlottesville, VA; [7]St. George's University of London and St. George's University Hospitals NHS Foundation Trust, London, UK; [8]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [9]Department of Neurology, University

of California, San Francisco, CA; [10]National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; [11]Feinberg School of Medicine, Northwestern University, Chicago, IL.

Corresponding Author Contact Information:

Abhishek G. Sathe, MS, PhD Candidate,

Center for Orphan Drug Research/Experimental and Clinical Pharmacology

Rm 4-226, McGuire Translational Research Facility

2001 6th St. SE

College of Pharmacy, University of Minnesota

Minneapolis, MN 55455 USA

Cell: +1617-650-4621

Email: sathe134@umn.edu

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Summary

The Established Status Epilepticus Treatment Trial was a blinded, comparative-effectiveness study of fosphenytoin, levetiracetam, and valproic acid in benzodiazepine-refractory status epilepticus. The primary outcome was clinical seizure cessation and increased responsiveness without additional anticonvulsant medications. Weight-based dosing was capped at 75 kg. Hence, patients weighing > 75 kg received a lower mg/kg dose. Logistic regression models were developed in 235 adults to determine the association of weight ($\leq$ or > 75 kg) or ($\leq$ or > 90 kg), sex, treatment, and weight-normalized dose with the primary outcome and solely seizure cessation. The primary outcome was achieved in 45.1% and 42.5% of those $\leq$ 75 kg and > 75 kg, respectively. Using univariate analyses, the likelihood of success that for those > 75 kg (OR 0.9 (95% CI 0.54, 1.51)) or > 90 kg (0.85 (0.42, 1.66)), were not statistically different compared with those $\leq$ 75 kg or $\leq$ 90 kg, respectively. Similarly, other predictors were not significantly associated with primary outcome or seizure cessation. Our findings suggest that doses, capped at 75 kg, likely resulted in concentrations greater than those needed for outcome. Studies that include drug concentrations and heavier individuals are needed to confirm these findings.

Keywords: Weight-based dosing, dose-response, anti-seizure medications, ESETT, seizure cessation

INTRODUCTION

The Established Status Epilepticus Treatment Trial (ESETT), that completed enrollment in January 2019, was a multi-center, randomized, double-blind study to determine the best or worst second-line treatment among fosphenytoin (FOS), levetiracetam (LEV) and valproic acid (VPA) in patients with benzodiazepine-refractory status epilepticus (SE).[1] The primary outcome of the study was cessation of SE at 60 minutes after the start of study drug infusion without use of additional anti-seizure medication, as determined by absence of clinically apparent seizures and improved consciousness. Subjects aged $\geq$ 2 years that failed first-line treatment with benzodiazepines and continued to have seizures were included in this study.

To maintain the blind, the three drugs, FOS, LEV, and VPA, had to be administered in the same volume and infusion rate even though the drugs had different mg/kg doses.[2] The FOS product label recommends a maximum dose of FOS (pro-drug of phenytoin) of 20 mg phenytoin equivalents (PE)/kg and that the rate of intravenous administration should not exceed 150 mg PE per minute due to cardiovascular risks associated with rapid injection.[3] Given that the ESETT protocol fixed the infusion time as 10 minutes, dosing was capped at 1500 mg PE. As a result, all patients weighing $\geq$ 75 kg received the same capped dose of FOS (20 mg/kg, maximum 1500 mg PE). Similarly, weight-based dosing was also capped at 75 kg for LEV (60 mg/kg, maximum 4500 mg) and VPA (40 mg/kg, maximum 3000 mg).

Patients weighing more than 75 kg received a lower mg/kg dose, thus, lower drug exposure would be expected given the pharmacokinetic properties of these drugs. Therefore, we performed a secondary analysis to assess whether the odds of treatment success were lower in patients weighing more than 75 kg as compared to those up to 75 kg. Since a primary outcome failure could be a result of one or more of the following: (1) need for an additional anti-seizure medication before 60 minutes, (2) clinically apparent seizures at 60 minutes or (3) lack of improvement in consciousness and response at 60 minutes, we also evaluated the association of weight and other predictors with clinical seizure cessation alone at 60 minutes.

METHODS

ESETT was approved by institutional review boards for all participating institutions.[1] Of the 478 patients enrolled in ESETT, 48.2% of adults and 0.9 % of children weighed > 75 kg. Because of the low number of children receiving a fixed dose and the possibility of differing response rates within children and adults, the analyses were limited to those ≥ 18 years (n=249). Two patients were excluded because the study drug volume administered could not be determined. Among the 247 enrollments, 12 patients were enrolled more than once but only their first enrollments were used. Among the 235 unique adult patients, 132 (56.2%) failed the ESETT primary outcome. Of the 132 failures, 87 (65.9%) failed because they needed an additional anti-seizure medication prior to 60 minutes, 10 (7.6%) failed due to clinically apparent seizures at 60 minutes, and 35 (26.5%) failed because they did not show an improvement in responsiveness at 60 minutes despite clinical seizure cessation.

ESETT primary outcome as the dependent variable

The ESETT primary outcome was expressed as binary (0=treatment failure, 1=treatment success) and used as the dependent variable for the following logistic regression models:

Association of weight with primary outcome using univariate and multivariate analyses

Two logistic regression models were used to test the association of weight, as a binary predictor, with primary outcome using weight cut-offs of 75 kg and 90 kg, respectively. A 90 kg cut-off was chosen to examine the association for higher weight individuals more rigorously. A logistic regression model was also tested association of interactions of weight, sex and treatment with the primary outcome. The model included treatment group (FOS, LEV or VPA), sex (male or female) and weight as binary (≤ or > 75kg) with all the interaction terms (weight x treatment group x sex) as predictors of the primary outcome.

Association of weight-normalized dose and sex with primary outcome

Separate logistic regression models were built for FOS, LEV and VPA to test the association of weight-normalized dose in mg/kg as a continuous variable, sex (male or female) and the interaction of dose and sex with the ESETT primary outcome.

Association of weight, sex and treatment with <u>clinical seizure cessation without additional anti-seizure medication</u>

A logistic regression model was used to test the association of weight and other predictors with clinical seizure cessation without additional antiseizure medication. Adult ESETT patients whose seizures were terminated but failed the primary outcome due to lack of improved responsiveness at 60 minutes (n=35) were treated as successes. Clinical seizure cessation, as binary (1= success, 0= failure), was used as the dependent variable for this analysis. A logistic model with weight, as a binary (≤ or > 75kg), sex (male or female) and treatment group (FOS, LEV or VPA) with all interactions (weight x treatment group x sex) as predictors was used to test their association with clinical seizure cessation.

Significance was determined as an alpha level < 0.05. All the analyses were conducted using R (version 3.6.1), RStudio (version 1.2.5001) and SAS (version 9.4).

RESULTS

Distribution of weights

ESETT patients ≥ 18 years weighed from 36-157 kg and were approximately normally distributed with a mean of 76.7 kg and standard deviation of 18.9 kg (**Figure 1**). Of the 235 patients, 113 (48.1%) weighed > 75 kg and received the maximum doses. The overall success rate for the primary outcome was 45.1% in those ≤ 75 kg vs. 42.5% in those > 75 kg. Baseline characteristics of the adult population by weight group (**Supporting Information Table S1)** show that male patients were more likely to weigh > 75 kg (50% vs. 66.4%), but all the other baseline characteristics were evenly distributed between the ≤ 75 kg and > 75 kg groups, respectively.

Comparison of response rates between the weight-based dosing group and fixed dose group

The difference [95% confidence interval] in the response rates for those ≤ 75 kg vs. those > 75 kg were 3.1% [-20.5%, 26.6%] for FOS, -1.2% [-21.6%, 19.3%] for LEV and 6.4% [-16.1%, 28.9%] for VPA. None of the differences were statistically significant since the 95% confidence intervals included 0 for each drug.

Association of weight and other predictors with primary outcome using univariate and multivariate analyses

<u>Primary outcome vs. weight</u>: The odds of success were 10.1% lower (odds ratio of 0.9 (95% confidence interval of 0.54, 1.51)) for those > 75 kg compared to those ≤ 75 kg and 15.4% lower (odds ratio of 0.85 (95% confidence interval of 0.42, 1.66)) for those > 90 kg compared to those ≤ 90 kg. These differences were not significant since the 95% confidence intervals for the odds ratios included 1. Similarly, there was no statistically significant association with treatment success when sex, treatment group and interaction of weight with sex and treatment group were included in the model (**Table 1**).

<u>Primary outcome vs. sex and weight-normalized dose</u>: When each drug was modeled separately, the weight-normalized dose was not associated with success, nor was sex or the interaction of dose and sex (**Supporting Information Table S2**).

Association of weight, sex and treatment with clinical seizure cessation without additional anti-seizure medication

A total of 138 (59%) patients did not have clinical apparent seizures at 60 minutes without receiving additional anti-seizure medication (regardless of whether they were responsive to verbal commands or noxious stimuli). As seen from **Table 1**, weight (≤ or > 75 kg), sex (male or female), treatment group (FOS, LEV or VPA), and all the interaction terms (weight x sex x treatment group) did not have a significant association with clinical seizure cessation.

DISCUSSION

The results of these secondary analyses demonstrate that the differences in response rates between the fixed dosing regimen (above 75 kg) and weight-based regimen (up to 75 kg) were not significant when the study drugs were grouped together or analyzed separately. The logistic regression models using the ESETT primary outcome and clinical seizure cessation without additional anti-seizure medication as dependent variables also failed to find significant associations with weight, treatment, sex or weight-normalized dose.

Fixed dosing, which is commonly used in adults, results in lower doses per body weight in heavier individuals and potentially lower drug concentrations for many drugs. Furthermore, if drug concentrations fall in the linear portion of the dose-response curve, lower drug concentrations may result in reduced efficacy. In this study, while approximately half of the ESETT adult patients received the maximum dose, the response rates between weight-based and fixed dosing regimen were similar. It is possible that weight or weight-normalized dose did not affect the primary outcome or clinical seizure cessation because the doses used in the trial resulted in drug concentrations above those needed for therapeutic outcome even in patients above 75 kg. While this may be true, other predictors, such as drug concentration, would have been a better metric to evaluate the differences between responders and non-responders. We know that drug concentrations can be variable in individuals receiving an identical dose.[4–6] There is also evidence that the pharmacokinetics of FOS, LEV and VPA are altered in overweight and obese patients.[7–10] In particular, patients with higher body fat will likely have greater volume of distribution. However, we were not able to investigate the effect of drug concentrations or BMI as sufficient information was not available. Furthermore, only 18 (7.7%) patients weighed above 100 kg. Thus, differences in pharmacokinetics, if any, may not have been large enough to impact the outcome.

The ESETT primary outcome was a composite and included absence of clinically apparent seizures and improved responsiveness at 60 minutes. It is possible that those who had higher doses were more likely to stop seizing but also more likely to have no improvement in responsiveness. To tease out the association of weight and other variables with clinical seizure cessation alone, we included those who failed the primary outcome only due to the lack of improved responsiveness at 60 minutes as successes but found no significant differences between fixed and weight-based dosing. Future studies of status epilepticus will likely include EEG as a part of outcome and allow us to better understand this subgroup.

A limitation of these analyses is the small number of patients in each treatment group (~40/drug) weighing above 75 kg. The wide confidence intervals for the difference in response rates suggest that a larger sample size would be needed to confirm these findings. While these were secondary analyses, the adaptive study design was in fact powered adequately for the primary outcomes.

CONCLUSION

Weight-based dosing used in ESETT with a 75 kg cut-off does not appear to have an impact on the primary outcome or clinical seizure cessation. It is possible that the concentrations attained were above those needed for therapeutic outcome. However, studies with larger sample size and additional data (drug concentrations, BMI, etc.) are required to confirm our findings. Future studies which measure drug concentrations would allow exploration of exposure-response instead of dose-response relationships.

FIGURE LEGENDS

Figure 1: Distribution of ESETT adult patient weights and the response to the treatment administered as treatment success (blue) or treatment failure (red)

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CONFLICTS OF INTEREST

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GW Pharmaceuticals, Neurelis, Takeda, Medtronic and Cerebral Therapeutics. Dr. Lowenstein served on the Scientific Advisory Board of Bloom Science. The remaining authors have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Abhishek G. Sathe: https://orcid.org/0000-0002-7348-4208

James C. Cloyd: https://orcid.org/0000-0002-3607-6619

Robert Silbergleit: https://orcid.org/0000-0003-4101-2430

Jaideep Kapur: https://orcid.org/0000-0002-8608-1352

Hannah R. Cock: https://orcid.org/0000-0002-5656-0141

Nathan B. Fountain: https://orcid.org/ 0000-0003-2058-0308

Shlomo Shinnar: https://orcid.org/0000-0001-6714-3960

Daniel H. Lowenstein: https://orcid.org/0000-0002-5869-4020

Thomas P. Bleck: https://orcid.org/0000-0002-8267-9787

Lisa D. Coles: https://orcid.org/0000-0003-3613-9904

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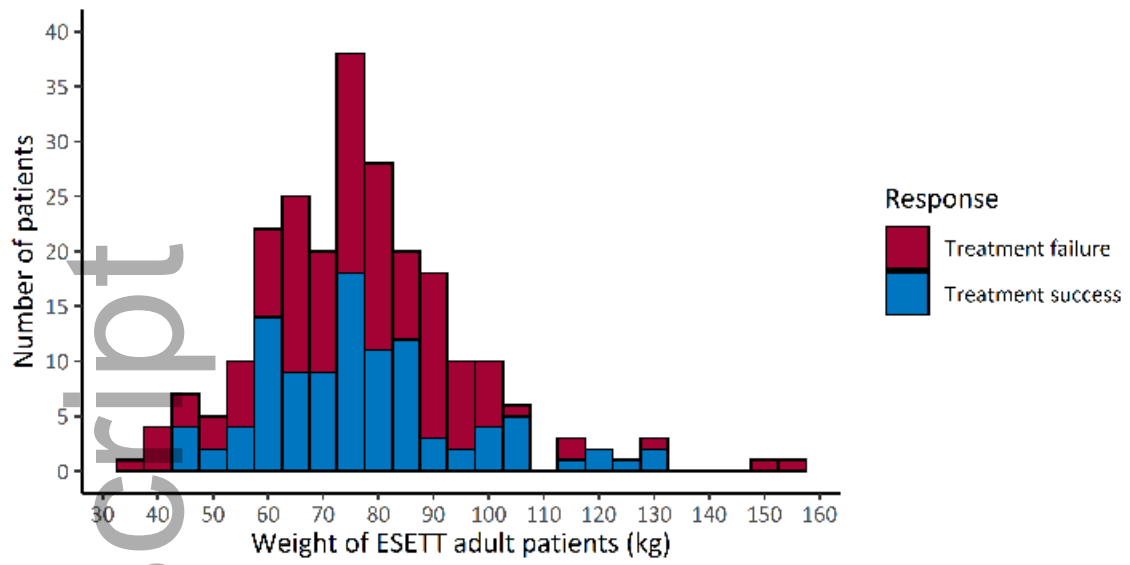
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Table 1: Logistic regression models of the probability of success using weight, treatment and sex with all interactions (weight ≤ 75 kg as reference group) (n=235)

Weight-group	Treatment	Sex	Using primary outcome as dependent variable Adjusted Odds Ratio (95% confidence interval)	Using clinical seizure cessation without additional anti-seizure medication as dependent variable Adjusted Odds Ratio (95% confidence interval)
> 75 kg	Fosphenytoin	Male	0.71 (0.20, 2.55)	0.56 (0.14, 2.26)
> 75 kg	Fosphenytoin	Female	1.13 (0.26, 4.94)	1.16 (0.27, 5.05)
> 75 kg	Levetiracetam	Male	0.82 (0.26, 2.56)	0.47 (0.15, 1.49)
> 75 kg	Levetiracetam	Female	1.70 (0.45, 6.44)	1.08 (0.29, 4.08)
> 75 kg	Valproic acid	Male	0.83 (0.26, 2.66)	0.72 (0.22, 2.40)
> 75 kg	Valproic acid	Female	0.64 (0.14, 2.91)	0.49 (0.11, 2.20)

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