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Article type : Brief Communication (includes Case Reports)

Title: Response to antiseizure medications in neonates with acute symptomatic seizures

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/EPI.14671

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Key Words: Neonatal Seizures; EEG; Electroencephalogram; Epilepsy; Neurocritical Care; Neonatal Encephalopathy; Hypoxic-Ischemic Encephalopathy; Seizure; Anti-Epileptic Drug; AED

Short Title: Response to treatment for neonatal seizures

Abbreviations and Acronyms: ACNS = American Clinical Neurophysiology Society; EEG = electroencephalogram; continuous EEG (cEEG); HIE = hypoxic-ischemic encephalopathy; IQR = interquartile range; OR odds ratio; CI confidence interval

Summary

In a prospective cohort of 534 neonates with acute symptomatic seizures, 66% had incomplete response to the initial loading dose of antiseizure medication (ASM). Treatment response did not differ by gestational age, sex, medication, or dose. The risk of incomplete response was highest for seizures due to intracranial hemorrhage and lowest for HIE although the difference was not significant after adjusting for high seizure burden and therapeutic hypothermia treatment. Future trial design may consider testing ASMs in neonates with all acute symptomatic seizure etiologies and could target neonates with seizures refractory to an initial ASM.

Introduction

Acute symptomatic neonatal seizures are often refractory to first-line anti-seizure medications (ASMs). In the 1999 clinical trial of phenobarbital versus phenytoin, seizures recurred in >50% of neonates following the first loading dose of either medication, and neonates with higher seizure burden were less likely to respond.[1] Little is known about additional characteristics associated with initial treatment failure, although we previously showed that preterm and term neonates were equally likely to have persistent seizures after a loading dose of phenobarbital[2] and there was no difference in treatment response to initial doses of phenobarbital, phenytoin, or levetiracetam as the first line ASM.[3]

We hypothesized that treatment response to ASMs would not differ by seizure etiology and that treatment response would be dose dependent. Confirming these hypotheses provides important evidence for clinical care and data to inform future clinical trial design.

Methods

This prospective, observational cohort study included neonates with acute symptomatic seizures due to HIE, ischemic stroke (arterial or venous), or intracranial hemorrhage (ICH) treated at the nine sites of the *Neonatal Seizure Registry* (*NSR*). Each site has a level IV neonatal intensive care unit and follows the American Clinical Neurophysiology Society (ACNS) guidelines for continuous electroencephalography (cEEG) in neonates.[4]

Two prospective cohorts were merged: (1) *NSR,* a consecutive cohort of *all* neonates with seizures diagnosed clinically and/or with EEG confirmation enrolled 01/2013-11/2015 (waiver of consent); and (2) *NSR-II*, a non-consecutive cohort of neonates with acute symptomatic seizures diagnosed clinically and/or with EEG confirmation enrolled from 07/2016-03/2018 who survived the neonatal hospital admission (required written parental informed consent; *NSR-II*). The local institutional review board for every site approved the studies. Neonates from the initial *NSR* cohort were previously reported.[2,5,6]

Neonates were included for if they received a loading dose of an ASM, and adequate documentation regarding response to the loading dose was available. Neonates with events that were determined *not* to be seizures based on history, semiology, or cEEG were not enrolled. Inclusion of neonates with clinical events suspected to be seizures but without seizures confirmed on the study site EEG was at the discretion of the site investigator and considered if: (1) events treated with ASMs and (2) the clinical history, event semiology or referring hospital EEG supported the diagnosis of seizures. Study site investigators determined the primary seizure etiology based upon systematic medical record review. A neonate was considered to have incomplete response if electrographic seizures were documented >30 minutes after the initial load of medication was complete. The data collected could not be used to differentiate between incomplete and absent response to ASMs.

Seizures were defined as sudden, abnormal EEG events with repetitive and evolving pattern with minimum amplitude of 2μV and duration ≥10 seconds and were not required to have to have a clinical correlate.[7] Seizure exposure was extracted from cEEG reports at the study center and was categorized as follows: (1) high burden: status epilepticus, frequent recurrent seizures without status epilepticus, many ($\geq$7) isolated seizures, and (2) low burden: <7 seizures.[8]

Seizure treatment, including ASM selection and determination of loading dose, was at the discretion of the provider. No study-specific treatment guideline was provided, although seven of the nine sites had institutional guidelines, pathways, or workflows for seizure management. Initial EEG background was determined by the study site investigator based on the EEG report available for 253 neonates and was categorized as: (1) normal or (2) abnormal (including burst-suppression).

Descriptive statistics and results of *t*-tests and chi-square tests are presented. Multivariate logistic regression was used to build an adjusted model (initial inclusion $p \leq 0.1$, final model inclusion adjusted $p<0.1$). EEG background was only available for a subset of participants, and, therefore, was not included in the analysis. Confidence intervals were calculated using pairwise comparison of 95% confidence intervals. Analyses were completed using Stata 14 (StataCorp, College Station, TX).

Results

From 01/2013-03/2018, 534 neonates were enrolled (5 neonates were excluded for unknown loading dose, 1 for unknown response, 1 for initial medication not known). EEG recording duration was a median of 72 (interquartile range 45.7, 99.3) hours. **Table 1** presents the patient characteristics. Overall, 354 neonates (66%) had an incomplete response to the initial loading dose of ASM. There was no significant difference in the response by treating institution (p=0.2) although the range was broad (56%-81%); 95% confidence intervals suggested at most a difference of 52% between the highest and lowest centers with incomplete response.

Clinical Risk Factors for Incomplete Response

Incomplete response to the first loading dose of ASM was highest for neonates with seizures due to ICH 82/108=76%, as compared with HIE 175/284=62% and stroke 97/142=68%, p=0.02. There was no significant difference by sex (male 203/306=66% *vs* female 151/228=66%, p=0.98).

When comparing gestational age (GA) at birth, incomplete response was highest for extremely preterm neonates (13/16=81% for extremely preterm <28 weeks GA *vs* 6/12=50% for very preterm 28 to <32 weeks GA *vs* 30/51=59% for moderate/late preterm 32 to <37 weeks GA *vs* 305/455=67% for term ≥37 weeks GA), however the differences were not significant (p=0.2).

There was a higher chance of incomplete response to the initial dose of medication for neonates with higher electroencephalographic seizure exposure (status epilepticus 97/100=96%, frequent recurrent seizures 125/140=89%, ≥7 isolated seizures 72/94=72% *vs* <7 seizures 60/198=30%, p<0.0005), although the seizures occurring before *vs* after ASMs was not known.

Among term neonates with HIE, those who were *not* treated with therapeutic hypothermia were more likely to have an incomplete response than those who were cooled (78/105=74% among those not treated with therapeutic hypothermia *vs* 77/143=54% among those who were, p<0.001).

Treatment Response by ASM

Phenobarbital was the initial loading medication for 95% of participants. Incomplete response to the initial loading dose of the ASMs was similar (phenobarbital 336/508=66% *vs* levetiracetam 14/21=67% *vs* fosphenytoin 4/5=80%, p=0.8), however the number of neonates who received levetiracetam or fosphenytoin was very small. Difference in response by initial ASM was at most 49% using 95% confidence intervals with fosphenytoin performing worst.

There was no significant difference in loading dose measured in mg/kg for phenobarbital (mean loading dose was 19.9 ± 4.4mg/kg with incomplete response *vs* 19.3±3.2mg/kg for neonates with complete response p=0.096). Similarly, there was no significant difference for levetiracetam (34.5±18.0mg/kg with incomplete response *vs* 24.5±5.7mg/kg with complete response p=0.2) and fosphenytoin (20.0±4mg/kg for neonates with incomplete response vs 20.0mg/kg for the single neonate with complete response p>0.99, **Figure 1**), however the numbers of neonates who received levetiracetam and fosphenytoin was very small.

Relationship Between EEG Background and Treatment Response

Among 253 neonates with cEEG background reports available for analysis, the risk of incomplete response was higher for those with abnormal inter-ictal EEG (159/234=68%) as compared to those with normal inter-ictal EEG (9/19=47%, relative risk 1.4, 95% confidence interval 0.9-2.3, p=0.07).

Multivariable Analysis

After adjusting for high seizure burden and therapeutic hypothermia, seizure etiology was no longer significantly associated with likelihood of response to ASM (ICH odds ratio, OR, for 1.5, 95% confidence interval, CI 08-2.6, and ischemic stroke OR 0.8, 95% CI 0.5-1.5 when compared with HIE, p=0.2), whereas high seizure burden (OR 15.9, 95% CI 10.1-25.0, p<0.0005) and therapeutic hypothermia (OR 0.5, 95% CI 0.3-0.9, p=0.01) remained very highly associated with ASM response.

Discussion

In this large, prospective, multi-center study of neonates with acute symptomatic seizures due to the three most common neonatal seizure etiologies (HIE, ischemic stroke, or ICH), the rate of incomplete response to the first loading dose of ASM was very high (66%). Risk factors for

incomplete response included lack of therapeutic hypothermia treatment and high electrographic seizure burden.

It has been twenty years since a trial of phenobarbital versus phenytoin for initial neonatal seizure management reported that standard loading doses control seizures in fewer than half of infants.[1] Since then, more than 15 new ASMs have come to market for epilepsy management. Many new drugs are not suitable for critically ill neonates, yet even ASMs that may be appropriate (i.e., drugs with intravenous formulations such as levetiracetam, lacosamide, and brivaracetam) have not been studied in neonates in published randomized and controlled clinical trials. Case reports and case series of levetiracetam have established pharmacokinetics[9,10] and suggest that it is safe and may be effective for newborns with seizures.[10-12] A clinical trial of phenobarbital versus levetiracetam is complete, but the results have not yet been published. Animal studies of bumetanide combined with phenobarbital as a rational synergistic therapy show some promise; however, a small clinical trial was inconclusive.[13]

Barriers to neonatal seizure treatment trials include relatively rare incidence of the condition, the need for rapid consent, enrollment and randomization, lack of widespread cEEG availability, and uncertainty regarding optimal outcome measures. Clinical trials are needed not only to determine the most effective ASM and dose, but also to examine treatment approaches. Such approaches include the value and optimal use of cEEG and determining whether speed of effective treatment influences seizure response or long-term neurodevelopmental and epilepsy outcomes. Our results suggest that, in planning efficient neonatal clinical trials of ASMs, investigators could consider broad entry criteria (e.g., including late preterm infants, as well as neonates with HIE, ischemic stroke, and ICH), but might need to stratify by therapeutic hypothermia treatment, pretreatment seizure burden, and initial EEG background. Our data underscore the need to test new medications in neonates with seizures refractory to an initial ASM, who are the majority of those with seizures, usually have a higher seizure burden, and in whom improved treatment is more likely to have an impact on long-term outcome.

Although we present a large, multicenter cohort, our data have limitations. First, our *NSR-II* cohort excluded children who died during the neonatal admission and included non-consecutive neonates. Therefore, it may be enriched for less severely affected infants. Second, incomplete

response to ASM was defined as seizure recurrence >30 minutes after the initial loading dose While most treatment failures occur within the first hours after a loading dose of ASMs, we cannot exclude that seizures recurred more than 24 hours after the loading dose given that study sites monitored neonates for a minimum of 24 hours after the last electroencephalographic seizure as per ACNS guidelines. Third, seizure exposure was measured using counts rather than other approaches (e.g. percent of the record comprised of seizures). Fourth, seizure exposure prior to the medication load was not universally available, so we cannot differentiate between seizures occurring before versus after the initial loading dose, however our findings are in keeping with the results of the Painter trial, which also showed a relationship between seizure burden and response to ASM. Fifth, the time from seizure recognition to treatment was not measured, and this timing might modify treatment response. Nonetheless, the results echo published data that suggest higher seizure exposure is associated with lower likelihood of complete treatment response.[1] Sixth, use of ASMs was not randomized, and therefore it is difficult to interpret any similarities or differences by ASM.

Conclusions

Incomplete response to ASM is expected for most neonates with acute symptomatic seizures who receive current standard treatment approaches, regardless of etiology, GA, initial ASM, and loading dose. This finding underscores the need for novel treatment approaches and suggests that future trials focused on ASM efficacy may be efficiently designed by stratification or exclusion of lower risk groups and could include all acute symptomatic etiologies of seizures, particularly those with seizures refractory to an initial ASM.

Table 1: Clinical characteristics of 534 prospectively enrolled infants with acute symptomatic neonatal seizures.

	Total N=534
Male	306 (57%)
Term	455 (85%)

Seizure etiology	
- Hypoxic-ischemic encephalopathy	284 (53%)
- Ischemic Stroke	142 (27%)
- Intracranial hemorrhage	108 (20%)
Initial ASM used as a loading dose	
- Phenobarbital	508 (95%)
- Levetiracetam	21 (4%)
- Fosphenytoin	5 (1%)

Data are presented as N (%)

Figure 1: Response to ASM for 534 neonates with acute symptomatic seizures stratified by medication and dose. Response did not vary by medication (incomplete responses: phenobarbital 336/508=66% *vs* levetiracetam 14/21=67% *vs* fosphenytoin 4/5=80%, p=0.8)

Acknowledgement

The Pediatric Epilepsy Research Foundation and the Patient Centered Outcomes Research Institute supported this study but did not participate in design or conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The authors would like to acknowledge Drs. Donna Ferriero and Faye Silverstein for their contributions to the *Neonatal Seizure Registry*, as well as the research assistants and parent partners at each study site.

Ethical Publication

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.

Conflict of Interest Statement

Hannah C. Glass, MDCM, MAS has nothing to disclose.

Janet S. Soul, MDCM receives royalties from UpToDate.

Catherine J. Chu, MD has nothing to disclose.

Shavonne L. Massey, MD has nothing to disclose.

Courtney J. Wusthoff, MD, MS has served as a paid consultant for Ceribell and Persyst.

Taeun Chang, MD has nothing to disclose.

M. Roberta Cilio, MD, PhD received research funding from Insys Development Company, paid to her Institution, for company sponsored trials. She has been a consultant for BioMarin Research Inc., and for GW Pharmaceuticals Inc

Sonia L. Bonifacio, MD has nothing to disclose.

Nicholas S. Abend, MD MSCE has nothing to disclose.

Cameron Thomas, MD, MS has nothing to disclose.

Monica Lemmon, MD has nothing to disclose.

Charles E. McCulloch, PhD has nothing to disclose.

Renée A. Shellhaas, MD, MS is a consultant for the Epilepsy Study Consortium and receives honoraria from UpToDate for neonatal seizures topics.

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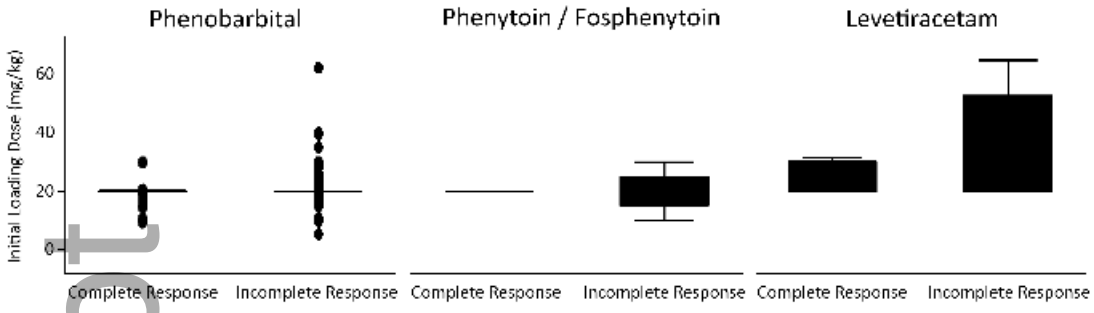

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