Standardized approaches to the treatment of neonatal seizures remain undeveloped. We assessed the type and number of anticonvulsants selected, blood levels attained, and postdischarge anticonvulsant treatment of neonatal seizures among five neonatal intensive care units in the United States between 2000-2003. Almost all of the 480 neonates (94%) with seizures were treated, initially with phenobarbital (82%), lorazepam (9%), phenytoin (2%), other anticonvulsants (1%), or a combination of the first two drugs (6%). While the majority of neonates were treated with one drug (59%), the number of anticonvulsants varied ($P < 0.0001$), as did the peak serum phenobarbital levels ($P < 0.0001$). The majority (75%) of survivors received anticonvulsant treatment after discharge. These neonates were more likely to have had abnormal electroencephalography or brain imaging, or to have needed a second anticonvulsant, compared with neonates whose drug therapy was discontinued. Anticonvulsant therapy is used in the majority of neonates with seizures, mostly with phenobarbital, and treatment is continued beyond discharge. The observed wide therapeutic variability may reflect a lack of standardized diagnostic and treatment approaches, particularly for seizures refractory to initial phenobarbital therapy. Trials of anticonvulsants with long-term neurodevelopmental follow-up are needed to develop evidence-based treatment guidelines. © 2007 by Elsevier Inc. All rights reserved.


Introduction

Seizures occur more often in the neonatal period than at any other time during the human lifespan, and reported incidence rates range between 1-4 per 1,000 live births [1-4]. Neonatal seizures are associated with high mortality and morbidity, and their ultimate outcome depends more on the underlying etiology rather than on gestational age [5,6]. Morbidity manifests as cerebral palsy, epilepsy, or long-term neurofunctional deficits in memory, behavior, and cognition because of disturbed neural connectivity, and changes in receptor composition and dendritic structure [6-8]. Neonatal seizures themselves may cause injury and exacerbate existing brain damage [9]. Based on this, immediate and aggressive anticonvulsant therapy would seem reasonable. However, animal studies suggest that the most commonly used neonatal anticonvulsants might have deleterious effects on the developing brain [10,11], and long-term human studies indicated cognitive and learning impairment after prolonged treatment with phenobarbital [12,13]. Because neonatal seizures are often self-limited, it has been reasoned that perhaps not all seizures should be treated, or that anticonvulsant therapy should be discontinued quickly [14]. As the currently used anticonvulsants proved ineffective in achieving seizure cessation [15,16], the questions remain as to which anticonvulsant should be used (if at all), and how long the treatment should last to optimize neurodevelopmental outcome.

Currently, no guidelines exist regarding the diagnostic approach to neonatal seizures. In addition, there is a paucity of strong clinical evidence about the efficiency of anticonvulsants and their effects on neurodevelopment. As a result, therapeutic approaches have differed widely
among neonatal intensive care units. To lay the foundation for future multicenter studies, we sought to determine the areas of consensus or divergence in the treatment of neonatal seizures among geographically dispersed academic and community-hospital neonatal intensive care units in the United States.

Methods

This retrospective study was performed at three academic (Sites 1-3) and two community (Sites 4 and 5) neonatal intensive care units. The Institutional Review Boards for the protection of human subjects at all five institutions approved the chart review protocol.

Selection of Subjects

All newborns at less than or equal to 28 days of postnatal age, consecutively admitted during calendar years 2000-2003, were retrospectively identified from the admitting neonatal intensive care unit’s database, based on admission or discharge diagnoses of “neonatal seizures.” Their full medical records were reviewed (Fig 1). At Site 1, the neonatal intensive care unit’s database did not contain data on the presence of seizures. Consequently, the pharmacy database at Site 1 was used to identify all neonates who received phenobarbital for any reason during their stay. The subsequent review of the complete medical records ensured that only those neonates were entered into the study who received phenobarbital for documented seizures. Thus, the common-denominator inclusion criteria among the five sites for our final cohort were “treatment with phenobarbital” for “documented seizures.” “Documented seizures” included any electrographic seizure activity documented on electroencephalography, or any clinical motor activity documented as a seizure in the chart by the attending neonatologist at any time during the neonate’s stay or as the reason for transfer to the neonatal intensive care unit. Neonates from Site 1 were excluded from analyses that assessed seizure frequency, percent of neonates not treated with anticonvulsant, and type of anticonvulsants used, because neonates who were not treated or were treated with an anticonvulsant other than phenobarbital were not identified for this cohort. Based on the data from the other four sites, where 94-100% of treated neonates received phenobarbital, and based on the policy at Site 1, which favors phenobarbital use, we included this site when we assessed the number of anticonvulsants used above and beyond phenobarbital.

Data Abstraction

Medical records were reviewed using a standardized data-extraction sheet. The types and number of anticonvulsants used, blood levels attained, and whether or not treatment was continued beyond discharge from the unit were evaluated. Mortality was defined as death during the stay in the neonatal intensive care unit. Brain magnetic resonance imaging, computed tomography, and ultrasound reports were reviewed to determine neuroimaging characteristics. Electroencephalographic abnormalities were classified as electrographic (clinical or subclinical) seizures, or other nonseizure-related electroencephalographic abnormalities.

Settings

The five sites were similar in bed size and access to neurodiagnostic services, such as epileptology and neuroimaging. In addition, neonatal neurologists were available at the academic sites. The smaller community site, Site 4, opened in May 2001, and thus the study time period at that site was somewhat shorter compared to the other sites, i.e., 31 months instead of 48 months.

Statistical Analysis

Statistical analysis was performed using Stata 7 software (Stata Corp., College Station, TX). Variables were compared with unpaired t test and analysis of variance methods (for parametric data), or Mann-Whitney U and Kruskal-Wallis tests (for nonparametric data) between two or multiple groups for continuous variables, and with chi-square tests for categorical variables. Univariate analyses were adjusted for multiple comparisons. Statistical significance was defined as P < 0.05.

Results

Clinical Characteristics

The frequency of seizures recognized by clinical observation or standard electroencephalography was 2.9% (344/11,862) among the neonates admitted to the four sites that identified neonates based on documented seizures (Sites

![Figure 1. Flowchart of cohort formation. NS = neonatal seizure.](image-url)
Almost all neonates (94%; 322/344) received anticonvulsant treatment during their stay in the neonatal intensive care unit. Of the 322 neonates treated with an anticonvulsant, 313 (97%) received phenobarbital (Fig 1). Our final cohort included 480 neonates from all five sites who received phenobarbital for their clinical or electrographic seizures: 338 (70%) were admitted to academic sites, and 142 (30%) to community sites. Their clinical characteristics are presented in Table 1.

### Treated vs Untreated Neonates

Gestational age, birth weight, sex, ethnicity, inborn status, 5-minute Apgar score, need for mechanical ventilation, mortality, and type of admitting hospital did not differ between the groups of neonates who received anticonvulsant treatment (n/H11005 322; 94%) and neonates who were not treated (n/H11005 22; 6%). Neonates treated with anticonvulsants stayed longer in the neonatal intensive care unit (12 days vs 6 days; P/H11005 0.004), were more likely to have undergone a neuroimaging study (98% vs 91%; P/H11005 0.03), and were more likely to be diagnosed with global ischemia on neuroimaging (45% vs 10%; P/H11005 0.03) in the univariate analysis. These differences disappeared after adjustment for multiple comparisons.

### Choice of Anticonvulsants

Among the 322 neonates treated with anticonvulsants who were identified based on seizure occurrence at Sites 2-5, phenobarbital was the most common first-line drug (n/H11005 265; 82%), followed by lorazepam (n/H11005 30; 9%), phenytoin (n/H11005 6; 2%), and other anticonvulsants such as diazepam, clonazepam, valproate, and pyridoxine (n = 3; 1%). In 18 (6%) neonates, a combination therapy of phenobarbital and lorazepam (in four cases, along with phenytoin or diazepam) was used concomitantly as first-line treatment. The choice of first-line drug did not differ between sites, or between the academic and community settings, except for lorazepam, which was chosen more often in the academic units compared with the community units (20% vs 9%; P/H11005 0.005).

At Sites 2-5, 46% (147/322) of neonates received a second drug after failure to respond to the first anticonvulsant. Lorazepam was chosen in 50% (n/H11005 73) of these neonates, followed by phenytoin (39%; n = 59), phenobarbital (20%; n = 30), and other anticonvulsants (7%; n = 10). More than one anticonvulsant was given concurrently as second-line drug in 22 neonates. The choice of second-line drug was similar between sites and settings.

### Number of Anticonvulsants Used

Of the 344 neonates identified based on seizure occurrence at Sites 2-5, 22 (6%) did not receive any anticonvulsants (Fig 1). Of the final cohort of 480 neonates treated with phenobarbital at the five sites, 285 (59%) received only one anticonvulsant during their stay. No neonate was treated with more than four types of anticonvulsants (Table 2). Site 1 used phenobarbital as the first-line drug in 140 (84%) neonates, and 126 of those (90%) were not given any additional anticonvulsants. In comparison, Sites 2, 3, and 5 did not use any additional drug in 51/78 (65%), 30/57 (53%), and 65/117 (56%) of the neonates, respectively, whose first-line drug was phenobarbital. The num-

### Table 1. Clinical characteristics of newborns by type of setting

<table>
<thead>
<tr>
<th>Academic Hospitals</th>
<th>Site 1 (n = 167)</th>
<th>Site 2 (n = 103)</th>
<th>Site 3 (n = 68)</th>
<th>Total (n = 338)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>38 (23-44)</td>
<td>39 (23-42)</td>
<td>38 (23-42)</td>
<td>39 (23-44)</td>
<td>0.02</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>2950 (560-5800)</td>
<td>3140 (450-4900)</td>
<td>3060 (480-4480)</td>
<td>3060 (450-5800)</td>
<td>0.09</td>
</tr>
<tr>
<td>Male (n) (%)</td>
<td>97 (58)</td>
<td>61 (59)</td>
<td>32 (47)</td>
<td>190 (56)</td>
<td>0.2</td>
</tr>
<tr>
<td>Singleton birth (n) (%)</td>
<td>152 (92)</td>
<td>99 (96)</td>
<td>61 (90)</td>
<td>312 (93)</td>
<td>0.2</td>
</tr>
<tr>
<td>Length of stay (days)*</td>
<td>13 (2-181)</td>
<td>11 (0-177)</td>
<td>15 (1-215)</td>
<td>13 (0-215)</td>
<td>0.5</td>
</tr>
<tr>
<td>Mechanical ventilation (n) (%)</td>
<td>138 (83)</td>
<td>76 (74)</td>
<td>56 (82)</td>
<td>270 (80)</td>
<td>0.1</td>
</tr>
<tr>
<td>Born at study site (n) (%)</td>
<td>59 (36)</td>
<td>16 (16)</td>
<td>43 (63)</td>
<td>118 (35)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mortality (n) (%)</td>
<td>21 (13)</td>
<td>26 (25)</td>
<td>15 (22)</td>
<td>62 (18)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Community Hospitals</th>
<th>Site 4 (n = 13)</th>
<th>Site 5 (n = 129)</th>
<th>Total (n = 142)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>40 (28-43)</td>
<td>39 (24-42)</td>
<td>39 (24-43)</td>
<td>0.1</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>3300 (1210-4220)</td>
<td>3350 (480-5200)</td>
<td>3340 (480-5200)</td>
<td>0.9</td>
</tr>
<tr>
<td>Male (n) (%)</td>
<td>9 (69)</td>
<td>68 (53)</td>
<td>77 (54)</td>
<td>0.3</td>
</tr>
<tr>
<td>5-minute Apgar score*</td>
<td>8 (1-9)</td>
<td>7 (0-10)</td>
<td>7 (0-10)</td>
<td>0.7</td>
</tr>
<tr>
<td>Singleton birth (n) (%)</td>
<td>11 (85)</td>
<td>123 (95)</td>
<td>134 (94)</td>
<td>0.1</td>
</tr>
<tr>
<td>Length of stay (days)*</td>
<td>5 (1-56)</td>
<td>12 (1-148)</td>
<td>10 (1-148)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mechanical ventilation (n) (%)</td>
<td>5 (38)</td>
<td>79 (61)</td>
<td>84 (59)</td>
<td>0.1</td>
</tr>
<tr>
<td>Born at study site (n) (%)</td>
<td>8 (62)</td>
<td>35 (27)</td>
<td>43 (30)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mortality (n) (%)</td>
<td>1 (8)</td>
<td>21 (16)</td>
<td>22 (15)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Median (range).
Table 2. Variations in number of anticonvulsants used among sites

<table>
<thead>
<tr>
<th>Number of Anticonvulsants</th>
<th>Site 1 (n = 167)</th>
<th>Site 2 (n = 103)</th>
<th>Site 3 (n = 68)</th>
<th>Site 4 (n = 13)</th>
<th>Site 5 (n = 129)</th>
<th>Total (n = 480)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126 (75%)</td>
<td>51 (50%)</td>
<td>30 (44%)</td>
<td>13 (100%)</td>
<td>65 (50%)</td>
<td>285 (59%)</td>
</tr>
<tr>
<td>2</td>
<td>31 (19%)</td>
<td>35 (34%)</td>
<td>28 (41%)</td>
<td>0</td>
<td>61 (47%)</td>
<td>155 (32%)</td>
</tr>
<tr>
<td>3</td>
<td>10 (6%)</td>
<td>13 (13%)</td>
<td>9 (13%)</td>
<td>0</td>
<td>3 (2%)</td>
<td>35 (7%)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Median (range), by site*†</td>
<td>1 (1-3)</td>
<td>1 (1-4)</td>
<td>2 (1-4)</td>
<td>1</td>
<td>2 (1-3)</td>
<td>1 (1-4)</td>
</tr>
</tbody>
</table>

* Because of a policy at Site 4 that required all neonates who needed a second anticonvulsant to be transferred to an academic site, we did not compare the two community sites.
† P < 0.0001 between all sites; P < 0.0001 between the two academic sites; and P < 0.0001 between academic and community-based settings.

The number of anticonvulsants varied widely among the academic sites, and between types of settings. Due to the small sample size (n = 13) of the cohort at Site 4, removing this cohort from the analysis did not alter the results of the other comparisons.

Level of Anticonvulsants

Serum phenobarbital levels were collected from 367 (89%) of 413 neonates who received phenobarbital at four sites. For Site 3, anticonvulsant levels were not readily accessible by chart review. The distribution of peak serum phenobarbital levels was skewed (Table 3) toward higher levels at Sites 1 and 4, which favored the use of phenobarbital and where the least number of anticonvulsants was used (Table 2). The distribution of phenobarbital levels at Sites 2 and 5, which used more anticonvulsants, seemed to be more symmetric, with the majority of peak levels between 20-50 mg/L. The median peak levels varied among the sites (P < 0.0001), although this variation might not be clinically significant (Table 3).

Continuation of Anticonvulsant Treatment After Discharge

Of 376 survivors, 298 (75%) were discharged while on anticonvulsant therapy from the neonatal intensive care units. The percentage of neonates discharged while on an anticonvulsant varied among the five sites as follows: 77%, 82%, 57%, 92%, and 76% (P = 0.009). The ratio of neonates with continued anticonvulsant therapy was similar in the academic and community settings (74% vs 78%; P = 0.5). Continuation of anticonvulsant therapy was not associated with the neonates’ inborn status, gestational age, or type of hospital to which they were admitted (all P > 0.05). Clinical factors associated with postdischarge maintenance of anticonvulsants included the presence of clinical seizures in 238 (63%) of 376 neonates discharged while on anticonvulsant therapy, whereas electrographic seizures or nonepileptic abnormalities were detected on electroencephalography in 181 (48%) neonates, and neuroimaging abnormalities were documented for 188 (50%) neonates.

Neonates who were discharged while on an anticonvulsant were more likely to have abnormal electroencephalography (89% vs 68%; P = 0.001) or brain-imaging studies (72% vs 39%; P < 0.0001), or to need a second anticonvulsant (37% vs 26%; P = 0.03), than neonates whose anticonvulsant treatment ended before discharge.

Discussion

This multicenter study assessed anticonvulsant treatments of neonatal seizures in academic and community newborn intensive care unit settings. Although almost all neonates with recognized seizures received anticonvulsants, and three quarters of the cohort remained on an anticonvulsant drug regime beyond discharge from the neonatal intensive care unit, anticonvulsant treatment practices varied widely among sites and between the different types of setting, which may reflect variability in diagnostic approaches in addition to the current lack of standardized treatment protocols.

Uniformly at all settings, almost all neonates with documented seizures were treated with anticonvulsants, despite a lack of evidence that anticonvulsant treatment reduces neonatal mortality or long-term morbidity [17]. Our data confirm that there is a general unwritten consensus among clinicians that seizures should be treated, particularly if they are frequent or prolonged [18,19]. A possible explanation for the willingness to treat, rather than withhold treatment, is the evidence from animal and human studies that seizures disrupt cerebral metabolism and neuronal integrity, and result in subsequent impairment of learning, memory, and behavior, and reduce the seizure threshold later in life [20-23]. Clinical diagnosis of
neonatal seizures without electroencephalographic documenta-
tion is notoriously inaccurate. Therefore, neonates might receive treatment even in the absence of true seizures. We recognize that some of the “documented seizures” in this study might have included nonepileptic movements, in addition to electrographic seizure activity or true epileptic clinical seizures. Our goal was to assess real-life treatment scenarios at the tertiary care level. At present, the continuous clinical and electroencephalo-
graphic monitoring of neonates, even of those at high risk for seizures, is not part of the routine protocol in most neonatal intensive care units in the United States.

Another dilemma for clinicians when deciding whether or not to treat neonatal seizures in the first hours after observation is that even though the natural history of neonatal seizures is unknown, clinical and laboratory observations suggest that they may be most severe in the first week after birth, but subsequently self-resolve regardless of intervention [15,24,25]. Again, because of the lack of established, standardized diagnostic and treatment protocols, neonatal units in different hospitals, or even different neonatologists within the same unit, may set their treatment thresholds individually, based on their best clinical judgment, e.g., as to how many seizures justify treatment, whether clinical seizures need to be confirmed electrographically, what etiologic workup needs to be done, and how long the neonates will be treated. We did not follow our cohort; therefore, the postdischarge history of the seizures is unknown. While in the neonatal intensive care unit, neonates who did not receive anticonvulsants were similar to those who did receive them in most clinical characteristics, including mortality, and stayed in the unit for a shorter time. This is in contrast with another study, where 80% of untreated neonates with electrographically confirmed seizures were moribund and died [5].

Another similarity between sites was that phenobarbital remained the mainstay of treatment. Phenobarbital’s popularity is likely due to its good safety profile compared with other parentally available anticonvulsants, such as phenytoin and benzodiazepines [26]. The acute side effects of the latter drugs include hypotension, arrhythmia, sedation, and respiratory depression, which might lead to further cerebral hypoperfusion.

As the loading dose of phenobarbital was similar among our sites, the variability in peak phenobarbital levels might have been due to the different levels of maintenance doses given, depending on the unit’s policy concerning therapeutic endpoints before adding or switching to another anticonvulsant. The clinical endpoints for treatment of neonatal seizures are still elusive, and in the absence of diagnostic and therapeutic guidelines, even studies that lay the groundwork for future protocols used arbitrary definitions of seizure control, e.g., cessation of clinical seizure, or no electrographic seizure following the first dose of anticonvulsant, or an 80% reduction in severity of seizures on electroencephalography [15,27,28].

Likewise, the variability in number of anticonvulsants in our study may reflect similar differences in diagnostic approaches, in addition to differences in therapeutic endpoints. Some neonatal intensive care units without continuous electroencephalographic monitoring might treat seizures until the clinical components subside, while others treat more aggressively, until there is complete cessation of electrographic seizure activity.

Remarkably, over three quarters of the treated neonates in our cohort were discharged while on an anticonvulsant from their neonatal intensive care units, irrespective of type of setting, despite the potential adverse effects these drugs might have on the maturing brain [10,11]. The persistence of clinically evident seizures, which was present in about 60% of neonates, was the most common factor preceding continuation of anticonvulsant therapy, followed by abnormal neuroimaging and abnormal electroencephalographic findings, which suggests that the more neurologically abnormal neonates tended to be treated longer. Each site’s diagnostic resources and approach affected its ability to uncover the underlying etiology. It remains to be seen whether standardization of etiologic workup streamlines therapeutic decision-making. The risk of seizure recurrence in children after early withdrawal of anticonvulsant treatment of neonatal seizures is relatively small. Only 8% of children had recurrent seizures after being discharged from an academic hospital [29]. Other studies without early withdrawal of anticonvulsants reported an incidence of postneonatal seizures ranging between 20-28% [6,30]. Toddlers and school-age children who received long-term phenobarbital therapy exhibited later behavioral changes, impaired memory, and language and verbal development affecting reading and comprehension, compared with their peers who received a placebo [12,13,31].

Limitations

Only neonates in whom seizures were suspected during clinical observation or electroencephalography, and then documented in their medical records, were included in our study. Thus, because of the underlying issue which we aim to underscore in this study (i.e., the lack of standardized monitoring of high-risk infants and lack of guidelines to aid in the recognition of seizure activity), there probably were neonates whose clinical or electrographic seizures were missed. Thus, the true frequency of seizures could not be assessed. The 2.8% frequency rate of recognized seizures observed in our two academic sites, where neonates were selected based on primary seizure data, is lower than a published 4.5% rate of seizures diagnosed with a combination of clinical signs, amplitude-integrated electroencephalography monitoring, and standard electroencephalography in an academic neonatal intensive care unit [29]. However, the present study’s frequency of 2.8% is similar to the 2.3% reported rate of electrographically confirmed seizures [5]. Further, we might have failed to
include neonates who were sedated or pharmacologically paralyzed for ventilation, whose seizure activity was not detected due to uncoupling [32]. However, our main goal was to assess the real-life practices of experienced neonatal intensive-care staff who used standard clinical diagnostic criteria. Continuous electroencephalographic monitoring is still not the standard of care in the United States, even for high-risk neonates.

Conclusions

Whereas most neonates with suspected seizures receive anticonvulsant therapy and remain on treatment after discharge from the neonatal intensive care unit, current treatment practices vary widely, based on the unit’s local diagnostic and therapeutic policies. More prospective, randomized, controlled trials with subsequent long-term neurodevelopmental follow-up are needed to answer the questions of whether there is therapeutic benefit from anticonvulsants, which anticonvulsants should be used, and at what dose and how long the treatment should be continued.

We are indebted to the Neonatal Brain Disorders Center and Mureen Schlueter at the University of California at San Francisco, to Jill Maller-Kesselman, M.S., and Susan Delancy, M.S., at Yale University, to Varsha Mehta, Pharm.D., at the University of Michigan, and to Nancy Dolphin, RN, BSN, at Legacy Emanuel Children’s Hospital for assistance in data collection.

References


