Anticonvulsant Use and Outcomes After Intracerebral Hemorrhage

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Background and Purpose—There are few data on the effectiveness and side effects of antiepileptic drug therapy after intracerebral hemorrhage. We tested the hypothesis that antiepileptic drug use is associated with more complications and worse outcome after intracerebral hemorrhage.

Methods—We prospectively enrolled 98 patients with intracerebral hemorrhage and recorded antiepileptic drug use as either prophylactic or therapeutic along with clinical characteristics. Antiepileptic drug administration and free phenytoin serum levels were retrieved from the electronic medical records. Patients with depressed mental status underwent continuous electroencephalographic monitoring. Outcomes were measured with the National Institutes of Health Stroke Scale and modified Rankin Scale at 14 days or discharge and the modified Rankin Scale at 28 days and 3 months. We constructed logistic regression models for poor outcome at 3 months with a forward conditional model.

Results—Seven (7%) patients had a clinical seizure, 5 on the day of intracerebral hemorrhage. Phenytoin was associated with more fever (P = 0.03), worse National Institutes of Health Stroke Scale at 14 days (23 [9 to 42] versus 11 [4 to 23], P = 0.003), and worse modified Rankin Scale at 14 days, 28 days, and 3 months. In a forward conditional logistic regression model, phenytoin prophylaxis was associated with an increased risk of poor outcome (OR, 9.8; 1.4 to 68.6; P = 0.02), entering after admission National Institutes of Health Stroke Scale and age. Excluding patients with a seizure did not change the results. Levetiracetam was not associated with demographics, seizures, complications, or outcomes.

Conclusions—Phenytoin was associated with more fever and worse outcomes after intracerebral hemorrhage. (Stroke. 2009;40:3810-3815.)

Key Words: anticonvulsants ■ intracerebral hemorrhage ■ outcomes ■ seizures ■ neurocritical care

Intracerebral hemorrhage (ICH) is a neurological catastrophe and has the highest rates of morbidity and mortality among stroke subtypes. There are still major areas of uncertainty in ICH management, including the use of anticonvulsants and prophylaxis for seizures. Seizures are more common in hemorrhagic than ischemic stroke. A brief course of anticonvulsant therapy after lobar ICH may reduce the risk of early seizures.

The published incidence of seizures after ICH varies widely from <10%, 4,5 to 10% to 20%, 6 to >20%. Many seizures are detected only with electroencephalographic monitoring. There is a paucity of data on the effect of anticonvulsants, complications of therapy, and outcomes after ICH.

The data on antiepileptic drug (AED) use in acute neurological disease are inconsistent and there are few data on which to firmly base guidelines. Arguments in favor of prophylaxis include the high risk of early convulsive and nonconvulsive seizures, the potential adverse consequences of seizures on blood pressure and intracerebral pressure, and the proved efficacy of phenytoin (PHT) in preventing early seizures (although not necessarily improved outcomes) after severe traumatic brain injury. 8 Increased PHT exposure, however, is associated with worse cognitive and functional outcomes after subarachnoid hemorrhage 9 with fewer side effects after 3 compared with 14 days of prophylaxis. 10 Preventing seizures after ICH may not improve outcomes because seizures may not be independently associated with worse outcomes after adjustment for other predictors. 4,11 Additionally, AED use (especially PHT) might be associated with fever, and fever is associated with worse outcomes after ICH. 12 We tested the hypothesis that AED use is associated with an increased risk of fever and worse functional outcomes after ICH.

Methods

Study Population
We prospectively enrolled consecutive patients with ICH diagnosed clinically by a board-certified neurologist or neurosurgeon correlated...
with CT. Patients with ICH due to trauma, ruptured aneurysms, arteriovenous malformation rupture, vasculitis, and other structural lesions were excluded before enrollment. Clinical and laboratory data were prospectively recorded. The study was approved by the Institutional Review Board.

Data Collection
We prospectively recorded baseline, demographic, hospital course, and follow-up data onto standardized forms. Neurological status on admission was assessed with the National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale. ICH volume on admission was calculated with the abc/2 method. We recorded outcomes at 14 days or discharge, whichever was first, with the NIHSS and the modified Rankin Scale (mRS) and a follow up mRS at 28 days and 3 months with a standardized questionnaire, generally by phone. We defined a poor outcome as mRS of 4 (moderately severe disability, not independent), 5 (bedbound), or 6 (dead).

Medical Complications and Antibiotics
We prospectively recorded the presence of a core temperature ≥100°F (37.8°C) on Day 0 or Day 1 through Day 13. We prospectively recorded the occurrence of pneumonia (using criteria from the US Centers for Disease Control), bacteremia (positive blood cultures, excluding one sample consistent with a contaminant), ventriculitis (cerebrospinal fluid pleocytosis or presence of cerebrospinal fluid Gram’s stain and/or culture), deep venous thrombosis on routine weekly Doppler screening, pulmonary embolism (diagnostic CT angiography of the chest), or placement of an external ventricular drain. We electronically retrieved data specifying every administered dose of commonly used antibiotics (piperacillin–tazobactam, vancomycin, ceftriaxone, cefepime, ceftazidime). We typically use oxacillin in patients with an external ventricular drain for the prevention of ventriculitis.

Clinical Seizures and AED Use
We prospectively recorded AED administration for prophylactic (before any documented or clearly described clinical seizure activity) or therapeutic use given at our hospital or a referring facility. When a clinical seizure occurred, defined as a characteristic bystander description or documented by medical personnel, we prospectively recorded the date. We electronically retrieved data specifying every administered dose of PHT serum-free level (0.002 for all). LEV use or duration was associated with seizures or any demographic characteristics (P=0.03) or PHT and LEV prophylaxis, 22 (22%) who received PHT prophylaxis, and 6 (6%) who received both PHT and LEV prophylaxis.

Statistical Analysis
Categorical data were compared with χ². Two dichotomous variables were analyzed with Mantel-Haenszel estimates where appropriate. Nonnormally distributed data were compared with Mann-Whitney U or Kruskal-Wallis H as appropriate and groups are presented as median [Q1 to Q3]. Continuous data were analyzed with Student t test or analysis of variance (least significant difference technique for multiple comparisons) as appropriate. Correlations were tested with the Pearson coefficient. Logistic regression models were constructed to explore predictors of poor outcome. A forward stepwise method selected variables in descending strength of association with poor outcome (P≤0.05 to enter, P>0.1 to exit). We also constructed ordinal regression models to show the results were consistent across levels of the mRS. We considered P≤0.05 significant. Statistical calculations were made with standard commercial software (PASW Statistics Version 17; SPSS Inc, Chicago, Ill). Funding sources had no role in the conception of the project, collection of the data, statistical analysis, or decision to submit for publication.

Results
There were 98 patients in the sample. Demographics are shown in Table 1. There were 58 (59%) patients who did not receive either PHT or LEV prophylaxis, 12 (12) who received LEV prophylaxis, 22 (22%) who received PHT prophylaxis, and 6 (6%) who received both PHT and LEV prophylaxis. When demographic factors were compared between the groups of PHT prophylaxis, LEV prophylaxis or both PHT and LEV prophylaxis, only ICH volume was different (P=0.03). In post hoc analysis, the difference was due to differences between patients who received no AED prophylaxis and patients who received PHT (P=0.03) or PHT and LEV (P=0.03) prophylaxis.

AED Use
Summary data regarding AED use are shown in Table 2. A seizure was associated with more total administration of PHT, a longer duration of PHT use, and a higher mean PHT serum-free level (P=0.002 for all). LEV use or duration was not associated with seizures or any demographic characteristics (P>0.1 for all). Of 721 doses of LEV given, 593 (82%) were for 500 mg, typically given every 12 hours.

Other AEDs were used rarely. Six patients received gabapentin, one received oxcarbazepine (this patient had a history of epilepsy), and one received topiramate. No patient received valproate.

Seizures and EEG Monitoring
Forty-two patients (43%) had EEG monitoring (Table 2). In the 7 patients with a clinical seizure, 5 occurred on the day of ICH. One patient was found to have nonconvulsive seizures 5 days after ICH onset on EEG monitoring. (This patient was admitted with a 20-mL lobar hemorrhage, an admission Glasgow Coma Scale of 15, NIHSS of 8, and was monitored for depressed mental status after admission. Her seizures were successfully controlled with both PHT and LEV, but life support was withdrawn at the request of her family 17 days after ICH.) No patient had convulsive status epilepticus. Neither prophylactic PHT nor LEV use
was associated with a reduced risk of a seizure \((P>0.1)\). Seizures were not significantly related to any of the demographic variables in Table 1, although 3 occurred in patients with lobar hemorrhage.

Table 2. Seizures and Use of PHT and LEV

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%), Mean±SD or Median [Q1–Q3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical seizure</td>
<td>7 (7)</td>
</tr>
<tr>
<td>EEG monitoring indication</td>
<td></td>
</tr>
<tr>
<td>Depressed mental status</td>
<td>30 (31)</td>
</tr>
<tr>
<td>Clinically suspected seizure activity</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Routine screening</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Clinical brain death</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Days from ICH to EEG monitoring</td>
<td>2.4 [1.4–5.8]</td>
</tr>
<tr>
<td>PHT prophylaxis</td>
<td>28 (29)</td>
</tr>
<tr>
<td>Only given at referring hospital</td>
<td>7 (7)</td>
</tr>
<tr>
<td>PHT duration of administration, days</td>
<td>7 [3–14]</td>
</tr>
<tr>
<td>PHT mean free level, (\mu g/mL)*</td>
<td>1.31±0.44</td>
</tr>
<tr>
<td>LEV prophylaxis</td>
<td>18 (18)</td>
</tr>
<tr>
<td>LEV duration of administration, days</td>
<td>8 [2–23]</td>
</tr>
</tbody>
</table>

*One to 2 \(\mu g/mL\) is considered therapeutic.

AED Use, Fever, Hospital Complications, and Antibiotic Use

The number of febrile days was associated with a longer duration of PHT use (Figure, \(P=0.03\)) and total administered dose (\(P=0.04\)). The number of days febrile was associated with worse NIHSS at 14 days (\(P=0.01\)), but not with mRS at 14 days, 28 days, or 3 months (\(P>0.1\) for all). PHT use was not associated with pneumonia, bacteremia, use of an external ventricular drain, ventriculitis, deep venous thrombosis, or pulmonary embolism (\(P>0.1\) for all). PHT prophylaxis was
not associated with the dose or duration of use of antibiotics (P>0.1 for all). There was a trend toward fewer ventilator-free days (3 [0 to 14] versus 10 [2 to 14], P=0.06) in patients receiving prophylactic PHT. There were 3 adverse events prospectively recorded as related to phenytoin: one rash, one episode of hypotension with an intravenous infusion, and one new fever. LEV was not associated with fever, ventilator-free days, infectious complications, or antibiotic use (P>0.1 for all).

**Craniotomy**

A craniotomy was performed in 22 (22%) patients. Craniotomy was associated with ICH location (P=0.002). Of lobar hemorrhages, 11 (28%) had a craniotomy, whereas no thalamic hemorrhage did. Craniotomy was not associated with more frequent seizures, LEV use, NIHSS at 14 days or discharge (P>0.1), or mRS at any time point (P>0.05 for all).

**Outcomes**

PHT prophylaxis was associated with worse NIHSS at 14 days or discharge (23 [9 to 42] versus 11 [4 to 23]; P=0.003). Table 3 shows the variables that were associated with functional disability at 3 months in univariate analysis. Associations with outcomes at 14 days or discharge and 28 days were similar. Seizures were not associated with outcomes (P>0.1). LEV was not associated with outcomes (P>0.1).

When a forward conditional model for poor outcome (mRS 4 to 6) at 3 months was constructed from the variables in Table 3, NIHSS on admission, age, and PHT prophylaxis entered the model in that order (Table 4). An ordinal regression model with these variables yielded similar results. Results were similar when patients with a seizure were excluded from the model. Forcing LEV into the model did not statistically significantly add (P>0.1) to the predictive value. Forcing the number of days with fever into the model was not significant (P>0.2) but attenuated the effect of PHT prophylaxis on poor outcome (OR, 5.8; 95% CI, 0.7 to 43.4; P=0.09), whereas age and NIHSS remained significant. Forcing ICH volume into the model did not statistically significantly add to it (P>0.2). NIHSS was correlated with both ICH volume (0.39, P<0.001) and intraventricular hemorrhage (0.27, P=0.008). A model of previously validated predictors of poor outcome and PHT prophylaxis is shown in Table 5.

**Discussion**

These data demonstrate an association between PHT prophylaxis and more fever, worse clinical examination at 14 days or discharge, and a worse functional outcome at follow-up. Analyses of PHT and any AED were similar, implying that results were driven by the effects of PHT. Results were similar when patients with a seizure were excluded, so a seizure is unlikely to be a confounder. We confirmed some previous findings that clinical seizures usually occurred within 24 hours,20 were uncommon,4 and not associated with outcomes, implying that universal prophylaxis is unlikely to benefit most patients.

Our results generally parallel the results of the placebo arm of an industry-sponsored trial that found AED use was associated with worse 3-month functional outcomes.21 Like in our data, PHT was most commonly used AED. The similar results from 2 separate cohorts increase the likelihood that AED use, specifically PHT, leads to worse outcomes in patients with ICH. Both studies, however, were nonrandomized and are potentially limited by residual confounding.

Fever may explain some, but probably not all, of the association between AED use and worse outcomes. Both fever and PHT use are common after ICH. Longer duration of treatment and more PHT use were associated with more fever without confounding by infection or antibiotic use. The known associations of fever and worse outcome after ICH may be enough justification to limit prophylactic PHT use on the grounds of minimizing fever. Despite the clear statistical association, we only prospectively identified PHT as the cause of fever once, indicating there was usually another plausible clinical explanation.

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### Table 3. Variables Associated With mRS at 3 Months After ICH*

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit NIHSS, per point</td>
<td>1.2 (1.1–1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Loss of consciousness at ICH onset</td>
<td>16.8 (3.5–79.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admit Glasgow Coma Scale, per point</td>
<td>0.6 (0.5–0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH volume, per mL</td>
<td>1.04 (1.01–1.07)</td>
<td>0.004</td>
</tr>
<tr>
<td>PHT prophylaxis</td>
<td>7.2 (1.5–34.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>3.3 (1.9–9.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.04 (1.004–1.08)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

**The association between the variable and poor outcome (mRS 4–6, nonindependence or worse) at 3 months is shown.**

### Table 4. Logistic Regression Model for Nonindependence or Worse (mRS 4–6) at 3 Months*

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit NIHSS, per point</td>
<td>1.3 (1.2–1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.08 (1.02–1.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>PHT prophylaxis</td>
<td>9.8 (1.4–68.6)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Variables were selected in a forward stepwise fashion from the list in Table 3. Variables are listed in the order of entry into the model. No further variables entered the model. An ordinal regression model with mRS at 3 months as the outcome gave similar results. Forcing LEV prophylaxis into the model did not significantly add to the model (P>0.1).**

### Table 5. Logistic Regression Model for Nonindependence or Worse (mRS 4–6) at 3 Months*

<table>
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<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit NIHSS, per point</td>
<td>1.3 (1.1–1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.08 (1.02–1.15)</td>
<td>0.02</td>
</tr>
<tr>
<td>PHT prophylaxis</td>
<td>9.0 (1.2–68.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICH volume, per mL</td>
<td>1.001 (0.97–1.03)</td>
<td>0.9</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>1.2 (0.2–6.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>0.7 (0.02–17.4)</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**This model shows the effect of PHT prophylaxis on poor outcome at 3 months after correction for other known predictors. All variables were forced into the model.**
These data suggest that the effect of prophylactic PHT may be analogous to subarachnoid hemorrhage in terms of increased fever and worse functional outcomes.1,10 More patients received prophylactic PHT than had seizures clinically or on EEG monitoring, suggesting that clinicians were more concerned with seizures than potential toxicity from PHT.

Our rate of detection of nonconvulsive seizures was lower than other series.7,22 The reason for the discrepancy is not clear but may be due to differences in patient selection or EEG interpretation. Further research might examine EEG interpretations in this population with standardized nomenclature,23 although the interrater reliability of proposed terminology has not been clarified. If we underdiagnosed nonconvulsive seizures, the data should be biased toward a potential benefit of prophylactic AED therapy, not the results we found.

One series found AED therapy may reduce the recurrence of seizures after lobar ICH, but the most commonly used agent was phenobarbital.4 We did not use barbiturates because they may depress mental status, impair ventilator weaning, and have cognitive side effects. These data do not indicate an ideal AED for the intensive care unit, and we did not have enough data on AEDs other than PHT and LEV for a meaningful analysis.

Craniotomy might have accounted for some PHT use. Craniotomy might be associated with seizures because both are associated with lobar location, although we did not find this. Craniotomy was not associated with outcomes, as in a previous randomized trial,24 so it is unlikely to explain our results.

There are limitations to these data. Patients were not randomized to PHT therapy or not, and the association of PHT and larger ICH volume might explain some of the association of PHT with worse outcome. PHT prophylaxis, however, remained significantly associated with worse functional outcomes after correcting for NIHSS and age, a previously published model.7 The lack of significance of ICH volume, intraventricular hemorrhage, and infratentorial location in multivariate models may be due to confounding by the NIHSS. Our lack of a protocol for AED use after ICH reflects uncertainty. We did not prospectively examine cognitive outcomes, although these are an important component of recovery. We used daily maximum temperature to calculate the effect of fever, but automated temperature recording with more frequent measurements would likely be more accurate. Strengths of our data include prospective ascertainment of patients and complications, electronic retrieval of medication administration, and outcomes at multiple time points with validated scales at and after discharge. Prospective documentation of seizure activity and the indication for AED use also assisted in minimizing confounding in these observational data.

In summary, we found that prophylactic PHT use was associated with more fever and worse outcomes in patients with ICH. Seizures were less common than in many series, which likely reduced any potential benefits of prophylactic AED use. Future research might clarify protocols for the effective use and reporting of EEG monitoring, target specific populations at high risk for seizures after ICH (eg, lobar hemorrhage5–25 with depressed mental status), and examine protocols to minimize AED exposure in patients unlikely to benefit from therapy.

Acknowledgments
We acknowledge the team at the Enterprise Data Warehouse (EDW) that built the portal for automated retrieval of medication and laboratory data. The EDW is a joint project of Northwestern Memorial Hospital, the Northwestern Medical Faculty Foundation, and Northwestern University. Further information is available at edw.northwestern.edu.

Source of Funding
This work was departmentally funded.

Disclosures
A.M.N. has received past research funding from NovoNordisk, the Neurocritical Care Society, and the Northwestern Memorial Foundation for a separate project (ended July 2008) and current research support from Gaymar Inc and Astellas Pharma US for unrelated projects. A.M.N. received past personal compensation from EKR Therapeutics (ended 2008). S.U.S. has received personal compensation from UCB Pharma and Pfizer. M.P.M. has received personal compensation from UCB Pharma.

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Stroke. 2009;40:3810-3815; originally published online September 24, 2009; doi: 10.1161/STROKEAHA.109.559948

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