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Phenytoin Exposure Is Associated With Functional and Cognitive Disability After Subarachnoid Hemorrhage

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Background and Purpose—Phenytoin (PHT) is routinely used for seizure prophylaxis after subarachnoid hemorrhage (SAH), but may adversely affect neurologic and cognitive recovery.

Methods—We studied 527 SAH patients and calculated a “PHT burden” for each by multiplying the average serum level of PHT by the time in days between the first and last measurements, up to a maximum of 14 days from ictus. Functional outcome at 14 days and 3 months was measured with the modified Rankin scale, with poor functional outcome defined as dependence or worse (modified Rankin Scale ≥ 4). We assessed cognitive outcomes at 14 days and 3 months with the telephone interview for cognitive status.

Results—PHT burden was associated with poor functional outcome at 14 days (OR, 1.5 per quartile; 95% CI, 1.3 to 1.8; $P < 0.001$), although not at 3 months ($P = 0.09$); the effect remained (OR, 1.6 per quartile; 95% CI, 1.2 to 2.1; $P < 0.001$) after correction for admission Glasgow Coma Scale, fever, stroke, age, National Institutes of Health Stroke Scale ≥ 10 , hydrocephalus, clinical vasospasm, and aneurysm rebleeding. Seizure in hospital (OR, 4.1; 95% CI, 1.5 to 11.1; $P = 0.002$) was associated with functional disability in a univariate model only. Higher quartiles of PHT burden were associated with worse telephone interview for cognitive status scores at hospital discharge ($P < 0.001$) and at 3 months ($P = 0.003$).

Conclusions—Among patients treated with PHT, burden of exposure to PHT predicts poor neurologic and cognitive outcome after SAH. (*Stroke*. 2005;36:583-587.)

Key Words: critical care ■ phenytoin ■ subarachnoid hemorrhage

Seizures after subarachnoid hemorrhage (SAH) are a feared but uncommon (4% to 10%)^{1,2} complication, with most occurring soon after ictus. Associations with rebleeding,^{2,3} thick cisternal blood,² and poor outcome⁴ have been reported. In recent studies, seizures after aneurysm surgery are uncommon,⁵ especially in patients at low risk,⁶ but many clinicians still opt for prophylaxis with phenytoin (PHT) or fosphenytoin. PHT has been shown to prevent seizures after craniotomy,⁷ serum assays are readily available, and it is easy to administer. Preventing a seizure may prevent rebleeding,³ although in multivariate models seizures and rebleeding are not associated.⁸ Benefit from prophylaxis, however, assumes that seizures are harmful and PHT is harmless.

PHT⁹ and anticonvulsants in general¹⁰ may have serious side effects after aneurysm surgery. There are no data on the question of whether harm might follow in a dose-dependent manner. We sought to answer the question of whether exposure of patients to PHT after SAH was associated with

harm by using serum drug levels and duration of exposure within the first 14 days after SAH to quantify an acute “PHT burden” for each patient.

Subjects and Methods

Five hundred twenty-seven consecutive patients with SAH admitted to our neurological intensive care unit between July 1, 1996 and October, 2002 were prospectively enrolled in the Columbia University SAH Outcomes Project.^{11,12} The study was approved by the hospital’s institutional review board, and written informed consent was obtained in all cases. The diagnosis of SAH was established by computed tomography (CT) scan, or by xanthochromia of the cerebrospinal fluid. Patients with SAH caused by trauma, arteriovenous malformation, or vasculitis were excluded.

Clinical and Radiographic Variables

We prospectively recorded baseline demographic data (age, sex), medical history, and clinical features at onset. A study neurologist performed a neurologic and general medical evaluation on admission. Neurologic status on admission was assessed with the Glasgow Coma Scale (GCS),¹³ National Institutes of Health Stroke Scale,¹⁴

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and the Hunt–Hess scale.¹⁵ We also recorded the Acute Physiology and Chronic Health Evaluation (APACHE) 2 score¹⁶ and calculated a physiological subscore by subtracting the age, chronic health points, and GCS contribution from the total score. Admission and follow-up CT scans were independently evaluated by a study neurologist for the presence of hydrocephalus, global cerebral edema,¹⁷ subarachnoid blood (Hijdra SAH sum score),¹⁸ the presence of intraventricular, intraparenchymal or subdural blood, and the presence of cerebral infarction (based on a new lucency on CT scan obtained while in hospital, with or without a clinical deficit). We assessed whether patients had clinical symptoms of delayed cerebral ischemia or cerebral infarction attributable to vasospasm.¹²

Seizures during hospitalization were diagnosed by the attending neurointensivist as focal or generalized repetitive rhythmic jerking, with or without impairment of consciousness, unless a simultaneous electroencephalogram recording revealed no electrographic seizure activity. Nonconvulsive seizures are not considered in this report.

Neurological Intensive Care Unit Management

The neurological intensive care unit management of our patients has been described in detail previously.^{11,12} It is our protocol to administer 20 mg/kg of PHT or fosphenytoin to all patients on admission, and to continue with 5 mg/kg of PHT or fosphenytoin daily or in divided doses. We checked serum PHT levels daily and adjusted the PHT dose as needed to maintain serum levels of 10 to 20 $\mu\text{g/mL}$. For patients who never had a seizure, the duration of PHT treatment was determined by the attending neurointensivist and neurosurgeon. Patients who had a seizure received PHT throughout the hospital course.

PHT Burden

Every PHT level for all 527 patients was electronically obtained from a computerized clinical information system, yielding 4221 PHT levels for analysis. “PHT burden” was defined as each patient’s average serum PHT level ($\mu\text{g/mL}$) multiplied by the time in days between the first and last measurements, up to a maximum of 14 days from ictus.

Follow-up Assessment

Follow-up assessments were conducted at 14 days after ictus (or hospital discharge, whichever came first) and 3 months after ictus. Functional outcome was assessed with the modified Rankin Scale (mRS),¹⁹ with poor outcome defined as mRS ≥ 4 (functional dependence or worse). At discharge and 3 months, we assessed cognitive outcome with the telephone interview for cognitive status (TICS),²⁰ a 10- to 15-minute telephone-administered test of global cognitive function ranging from 51 (best) to 0 (worst).

Statistical Analysis

Statistical analyses were performed with commercially available software (SPSS version 11, SPSS Inc). Continuous normally distributed variables were tested using ANOVA, and non-normally distributed continuous variables were tested using the Mann–Whitney *U* or Kruskal–Wallis *H* test. Post hoc comparisons of means were corrected with the least significant differences technique. Forward conditional methods were used to identify independent predictors of poor functional outcome in a logistic regression model. For prediction of TICS after correction for Hunt–Hess grade, we used a generalized linear model. For logistic regression models, we divided PHT burden into quartiles (≤ 37.19 , 37.2 to 81.79, 81.8 to 133.6, and ≥ 133.7), Hijdra sum score into quartiles (0 to 8, 9 to 15, 16 to 21, and ≥ 22), GCS into terciles (3 to 10, 11 to 14, and 15) and we defined a high admission National Institutes of Health Stroke Scale score as the top quartile (≥ 10), because these variables were not normally distributed and would have violated the assumptions of the analysis. For the change in TICS scores from discharge to 3 months, we used a repeated measured ANOVA. Significance was judged at $P \leq 0.05$.

TABLE 1. Baseline Characteristics of the Patients

Women	360 (68)
Seizure <6 h of ictus	54 (10)
History of epilepsy	14 (3)
Hunt–Hess grade	
1 mild headache	147 (28)
2 severe headache	77 (15)
3 lethargy	166 (31)
4 hemiparesis	77 (15)
5 coma	60 (11)
Loss of consciousness at ictus	207 (39)
Any thick cisternal blood on admission CT	297 (56)
Admission Glasgow Coma Scale	14 [10–15]
APACHE physiology score	6 \pm 4
Aneurysm size, mm	9 \pm 6
Age, y	53.4 \pm 14.2
Hijdra SAH sum score	15 [8–21]

Data are mean \pm SD, median [interquartile range], or n (%).

Results

Admission characteristics are shown in Table 1. Two hundred eighty (53%) had a poor functional outcome at 14 days (mRS ≥ 4). There were 8 \pm 5 PHT measurements over a mean of 6.9 \pm 4.5 days; 69 (13%) patients were exposed to PHT for ≥ 14 days.

Seizures During Hospitalization

Twenty-seven (5%) patients had seizures in the hospital. Clinical variables associated with in-hospital seizures are listed in Table 2. A seizure in hospital was associated with a poor functional outcome at 14 days in a univariate analysis (OR, 4.1; 95% CI, 1.5 to 11.1; $P=0.002$) only.

PHT Burden

The mean PHT burden was 89.5 \pm 62.3, the mean PHT level was 13.2 \pm 4.2, and the mean time exposed to PHT was 6.9 \pm 4.5 days. Factors associated with higher PHT burden are shown in Table 3. Higher quartiles of PHT burden were correlated with higher quartiles of Hijdra sum score ($P<0.001$). Hunt–Hess grade 3 patients had the highest PHT burden (104.6 over 7.9 days), followed, in order, by grades 4

TABLE 2. Clinical Variables Associated With Seizures in Hospital in Univariate Analysis

Variable	No. (%)	OR (95% CI)	<i>P</i>
Seizure within 6 h of ictus	54 (10)	2.7 (1.0–7.0)	0.05
History of epilepsy	14 (3)	5.9 (1.5–22.9)	0.03
Subdural hematoma	22 (4)	11.2 (4.1–30.6)	<0.001
Stroke from vasospasm	73 (14)	2.7 (1.1–6.4)	0.04
Any stroke	198 (38)	2.5 (1.1–5.5)	0.02
Aneurysm rebleed	38 (7)	3.2 (1.1–8.9)	0.04
Hydrocephalus	173 (33)	2.7 (1.2–5.8)	0.02
Fever >101.5°F	287 (54)	11.1 (2.6–47.6)	<0.001
NIH Stroke Scale ≥ 10	129 (24)	2.6 (1.1–5.6)	0.02

TABLE 3. Clinical Variables Associated With Increased Phenytoin Burden in Univariate Analysis.

Variable	No. (%)	P*
Women	360 (68)	0.02
Seizure within 6 h of ictus	54 (10)	0.002
Subdural hematoma	22 (4)	0.001
Hydrocephalus	173 (33)	0.006
Any stroke	198 (38)	0.001
Stroke from vasospasm	73 (14)	0.006
Seizure in hospital	27 (5)	<0.001
Clipping/coiling/no repair	344 (65)/83(16)/100 (19)	<0.001
Fever >101.5°F	287 (54)	0.001
Any thick clot on CT	297 (56)	0.009
Clinical vasospasm	84 (16)	<0.001

*Mann-Whitney U test.

(103.4 over 8.3 days), 2 (80.5 over 6.3 days), 1 (78.0 over 5.8 days), and 5 (69.7 over 5.8 days). The highest recorded PHT level was higher in patients with a poor functional outcome (19.9 ± 6.6 versus 18.6 ± 7.8 ; $P=0.04$). In univariate analysis, higher PHT burden ($P<0.001$) and higher quartile of PHT burden (OR, 1.5 per quartile; 95% CI, 1.3 to 1.8; $P<0.001$) were associated with an increased likelihood of poor functional outcome at 14 days. There was a statistical trend between higher PHT burden and poor functional outcome at 3 months ($P=0.09$).

Multivariate Model of Poor Functional Outcome

We performed a forward conditional logistic regression model (Table 4) for variables associated with poor outcome at

TABLE 4. Factors Associated With Functional Dependence or Worse at Hospital Discharge in Univariate (all $P \leq 0.006$) and Multivariate Analysis (all $P \leq 0.01$) in Order of Selection for the Multivariate Model

Variable	Univariate	Multivariate
Glasgow Coma Scale/tercile	0.2 (0.1–0.3)	NS
Fever >101.5°F	7.1 (4.8–10.4)	2.9 (1.6–5.0)
Stroke of any cause	5.9 (3.9–8.9)	2.9 (1.6–5.0)
Age, y	1.04 (1.03–1.06)	1.05 (1.03–1.07)
NIHSS ≥ 10	29.2 (12.6–67.9)	19.7 (7.4–52.7)
PHT burden/quartile	1.5 (1.3–1.8)	1.6 (1.3–2.0)
Rebleeding of aneurysm	17.3 (4.1–72.7)	14.5 (1.7–121.5)
Clinical vasospasm	4.7 (2.6–8.5)	3.4 (1.6–2.1)
Hydrocephalus	8.3 (5.3–13.3)	2.5 (1.3–4.7)
Stroke from vasospasm	5.2 (2.7–9.9)	NS
Seizure in hospital	3.9 (1.5–10.7)	NS
Global cerebral edema	3.5 (2.2–5.7)	NS
Ictal unconsciousness	2.9 (2.0–4.3)	NS
Any thick clot on first CT	2.7 (1.9–3.9)	NS
Admit Hunt-Hess, grade	2.4 (2.0–2.9)	NS
Hijdra score, quartile	1.7 (1.4–2.0)	NS
APACHE 2 scale, point	1.3 (1.2–1.4)	NS
Length of stay, day	1.1 (1.05–1.2)	NS

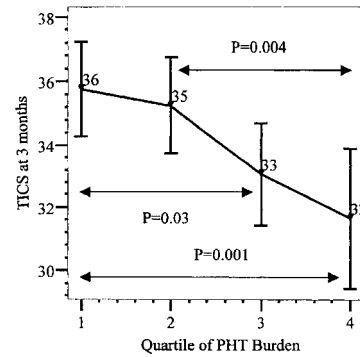


Figure 1. Relationship of quartile of PHT burden to TICS score at 3 months in 287 patients. Each successive increase in quartile of PHT burden was associated with a lower (worse) TICS score at 3-month follow-up. The means are different ($P=0.003$). Error bars represent 95% CI. Probability values shown are corrected with the least significant differences technique.

14 days. In order, tercile of GCS, fever >101.5°F, stroke, age, National Institutes of Health Stroke Scale ≥ 10 , quartile of PHT burden, rebleeding, clinical vasospasm, and hydrocephalus entered the model. Higher PHT burden increased the odds of poor outcome by 1.5 per quartile (95% CI, 1.2 to 1.9; $P<0.001$).

We forced length of stay into a model of poor outcome at 14 days with quartile of PHT burden. Quartile of PHT burden remained highly significant ($P<0.001$), whereas length of stay was no longer significant.

Cognitive Outcome

At 14 days, higher quartile of PHT burden was associated with worse performance on the TICS ($P<0.001$), even after correction for Hunt-Hess grade at admission ($P<0.001$).

TICS scores were available at 3 months for 287 patients (Figure 1). TICS scores improved from hospital discharge to 3 months ($P<0.001$), but patients in the highest quartile of PHT burden improved the most ($P=0.004$; Figure 2). Higher quartile of PHT burden remained associated with worse

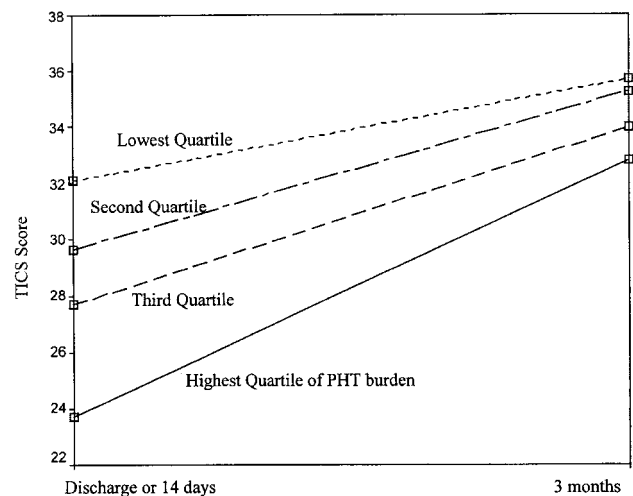


Figure 2. Change in TICS scores from hospital discharge (or 14 days) to 3 months. In all quartiles of PHT burden, TICS scores improved, but they improved faster over time in patients with highest quartile of PHT burden ($P=0.004$).

performance on the TICS ($P=0.003$), even after correction for Hunt–Hess grade on admission ($P=0.01$).

Discussion

We found that greater exposure to PHT was strongly associated with poor functional and cognitive outcome. The association between quartile of PHT burden and poor outcome did not change in the multivariate model, implying that the contribution of PHT burden is independent.

In the past, seizures and rebleeding were common and associated,³ leading to prophylaxis. Rates of seizures (now $\approx 5\%$)⁶ and rebleeds (now $\approx 7\%$)⁸ have greatly declined since then. We found that seizures were associated with poor functional outcome at 14 days, but they quickly dropped out of multivariate models. Thus, seizures are more likely a symptom of severe disease rather than an independent factor contributing to poor outcome.

It is possible that without routine PHT use, or with less aggressive use of PHT,²¹ we would have seen more seizures in our series. Although we attempted to capture all out-of-hospital seizures by careful history taking, we are likely to have missed some. In addition, we do not consider nonconvulsive seizures (electroencephalographic evidence of seizures without visible convulsions), a major source of morbidity after SAH.²²

Functional outcomes were significantly impaired by PHT exposure at 14 days, but not at 3 months, although a trend was found. Early functional disability is important, and may be the difference between discharge to home versus a rehabilitation facility, and between rehabilitation and a nursing home. This implies that some of the effects of increased acute exposure to PHT may be reversible. Another possibility is that global measures of functional outcome such as the mRS, which are heavily influenced by physical disability, may not be sensitive enough to detect persistent and clinically significant effects on neurologic function in the SAH population over time. Most patients after SAH do not have long-term physical disability, but rather report significant cognitive and emotional consequences. Therefore, tests of cognitive outcome, such as the TICS, may be more sensitive for detecting persistent disabilities.

The TICS may be the best single measure of cognitive outcome after SAH.²³ In our series, worse TICS scores were significantly associated with increased PHT exposure at 14 weeks and 3 months. PHT appears to impair cognitive recovery after neurotrauma,²⁴ so it is plausible that it impairs cognitive recovery after SAH, also. Patients with the highest quartile of PHT burden improved the most over time, which again implies that the effects of PHT on cognitive outcome may dissipate. Whether patients eventually achieve the same cognitive outcome regardless of PHT exposure remains unanswered. Unfortunately, we did have not data on PHT use after hospital discharge and therefore cannot analyze if continued PHT use had further cognitive implications. When the effects of PHT completely dissipate, if ever, is a major unanswered question, and longer-term follow-up will be required.

Our calculation of PHT burden may slightly underestimate PHT exposure because some patients were treated with PHT

at a referring hospital before transfer, and would not have an initial serum level that would appear in our data. We monitor PHT levels as long as the patient is receiving the drug and truncated the burden calculation at 14 days, so we were unlikely to systematically underestimate PHT burden near the end of hospitalization. In addition, there is unlikely to be a bias from sicker patients being monitored more often. Hunt–Hess grade 5 (comatose) patients actually had the lowest PHT burden, so it is unlikely that there is a bias from the sickest patients receiving the most PHT. The cumulative dose of PHT would be an alternative method for estimating PHT exposure.

Data on PHT exposure after 14 days were not available for analysis; therefore, any additional effects of PHT on 3-month outcome could not be determined. Few patients with seizures in hospital have epilepsy at follow-up,²⁵ and seizures in hospital do not usually lead to epilepsy after discharge.⁶ Even when survivors experience 1 seizure after discharge, they do not usually have a second.²⁶ In the past, long-term anticonvulsant therapy was recommended to prevent these late seizures.¹

Even though statistically correcting for complications associated with PHT burden did not decrease its significance on outcome, we cannot be sure there is no residual confounding. These concerns argue for a prospective study on the optimal dosage of PHT in a defined set of patients.

Free PHT levels may be more helpful than total PHT levels for assessing drug exposure. Free PHT levels are not as readily available to guide clinical decisions, however, and correlate well with total PHT levels overall.²⁷ We did not routinely obtain free PHT levels and therefore cannot report if a “free PHT burden” has the same effect.

All patients at our institution receive a loading dose of PHT. We cannot say whether any PHT is harmful, or whether forgoing PHT would lead to more seizures or worse outcome from seizures.

Animal models suggest that PHT may worsen neurological recovery after ischemic stroke.^{28,29} PHT may also cause fever, which is itself strongly associated with poor outcome and increased length of stay³⁰ in direct proportion to the length of time the patient is febrile.³¹ Fever after SAH is associated with poor outcome after correction for other prognostic variables.³²

Many clinicians today are using newer anticonvulsants instead of PHT, but available data are limited regarding their comparable efficacy in the acute hospital setting and their potential effects on neurologic recovery.³³ Drug levels for newer anticonvulsants are also more difficult to obtain than levels for PHT. Newer agents may not be better than PHT in the acute hospital setting, just more expensive and difficult to monitor.

Summary

Prophylactic PHT may contribute to poor functional and cognitive outcomes in a dose-dependent manner after SAH. These data suggest exposure to PHT after SAH should be minimized and argue for a prospective study of PHT use in patients at high risk for seizures after SAH.

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