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Results of Phase 2 Safety and Feasibility Study of Treatment With Levetiracetam for Prevention of Posttraumatic Epilepsy

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Objectives: To evaluate the safety and tolerability of treatment with levetiracetam and determine the trough levels of levetiracetam in patients with traumatic brain injury (TBI) who are at high risk for posttraumatic epilepsy (PTE).

Design: Open-label, nonrandomized phase 2 study with 2 arms comparing levetiracetam treatment vs observation.

Setting: Two level 1 trauma centers.

Patients: A total of 422 participants 6 years or older with TBI who have a 20% risk for PTE were screened. Of these participants, 205 (48.6%) were eligible. A total of 126 participants were enrolled: 86 adults and 40 children. A total of 66 participants were in the treatment group (46 adults and 20 children), and a total of 60 participants were in the observation group (40 adults and 20 children). Participants presenting within 8 hours after TBI received treatment, and those presenting more than 8 to 24 hours after TBI did not.

Intervention: Treatment with levetiracetam (55 mg/kg/d) for 30 days starting within 8 hours after injury.

Main Outcome Measures: Number of adverse events, mood score, number of infections, trough level of levetiracetam, and PTE.

Results: Of the 66 participants treated with levetiracetam, 2 (3%) stopped treatment owing to toxicity (somnolence). The most common adverse events were fatigue, headache, and somnolence. Mood scores and number of infections did not differ between the treatment and observation groups. Mean trough levels of levetiracetam on days 2 to 30 ranged from 19.6 to 26.7 µg/mL. At 2 years, 13 of 86 adults (15.1%) and 1 of 40 children (2.5%) developed PTE. At 2 years, 5 of 46 treated adults (10.9%) and 8 of 40 untreated adults (20.0%) developed PTE (relative risk, 0.47; $P=.18$).

Conclusion: Treatment with 55 mg/kg/d of levetiracetam (a dose with an antiepileptogenic effect on animals) for patients with TBI at risk for PTE is safe and well tolerated, with plasma levels similar to those in animal studies. The findings support further evaluation of levetiracetam treatment for the prevention of PTE.

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TRAUMATIC BRAIN INJURY (TBI) causes 5% of all cases of epilepsy in both children and adults.[1,2] There is no preventive treatment for epilepsy. Past attempts at preventing posttraumatic epilepsy (PTE) using antiepileptic drugs (AEDs) have been unsuccessful, probably because those older AEDs either had no antiepileptogenic effect in animal models (phenytoin sodium and carbamazepine) or had effects in doses too high and toxic for human use (phenobarbital sodium, valproate sodium, and clonazepam).[3,4]

Unlike previously tested AEDs, levetiracetam has had antiepileptogenic effects in animal models, in clinically applicable doses, with clinically relevant levetiracetam levels in blood (reviewed in Löscher and Brandt[5]). In a dose-dependent manner, it retards kindling with a true antiepileptogenic (vs anticonvulsant) effect in electrical limbic, pentylenetetrazole, corneal, and audiogenic rat and mouse models in a dose range of 13 to 54 mg/kg/d.[5] At 80 mg/kg/d, levetiracetam prevents epilepsy in a genetic model of epilepsy, the "spontaneously epileptic rat." In status epilepticus models of epileptogenesis, 50 to 300 mg/kg/d of levetiracetam attenuates the development of spontaneous seizures after self-sustaining status epilepticus induced by a 30-minute–long stimulation of the perforant pathway, although not after a 4-hour–long stimulation of the amygdala. In the kin-

dling and status epilepticus models, the same levetiracetam doses block increases in neuronal excitability and synchronization, 2 key processes of epileptogenesis. Other AEDs (such as phenobarbital, valproate sodium, lamotrigine, or clonazepam) lack these effects.

Levetiracetam has favorable side-effect and pharmacokinetic profiles in patients with epilepsy.[6] Patients with TBI, who often are critically ill, may differ from otherwise healthy patients with epilepsy in their susceptibility to adverse events and in the way that they metabolize the drug. The present pilot study evaluated the safety and tolerability and the pharmacokinetics of levetiracetam treatment of patients with TBI who are at high risk of PTE, defined as TBI with intracranial hemorrhage, penetrating wound injury, depressed skull fracture, or early posttraumatic seizure, with a dose that is antiepileptogenic in animals as a first step in evaluation of levetiracetam efficacy in PTE prevention. Although efficacy was not an outcome of the original study, we compare cases of PTE at 2 years after TBI between levetiracetam-treated and untreated groups. The pharmacokinetics results will be reported separately.

METHODS

STUDY DESIGN

This was a fixed-dose, open-label, nonrandomized phase 2 study with 2 arms comparing levetiracetam treatment vs observation at 2 level 1 trauma centers in Washington, DC: Children's National Medical Center and Washington Hospital Center. Both centers' institutional review boards approved the study. All participants or parents or legal surrogates signed the informed consent form before enrollment.

PARTICIPANTS

Children 6 years of age or older and adults were enrolled (age range, 6-87 years; 99 male participants and 27 female participants). Inclusion criteria were TBI with any intracranial hemorrhage, except for isolated subarachnoid hemorrhage, or with penetrating wound injury, depressed skull fracture, or early posttraumatic seizure. These criteria identify adult patients with an average 20% risk of PTE.[1] Exclusion criteria were a Glasgow Coma Scale score of less than 6, based on the best score within 4 hours of injury, to avoid high mortality; an elevated serum creatinine level (≥1.7 mg/dL for adults, ≥1.0 mg/dL for participants aged 13-17 years, and ≥0.7 mg/dL for participants aged 6-12 years [to convert to micromoles per liter, multiply by 88.4]); a history of psychosis, prior unprovoked seizure, cerebrovascular accident, TBI, or encephalitis within 3 years; AED use within 3 months; and unstable medical disease, moderate to severe mental retardation, or pregnancy.

Participants who met all inclusion criteria except for presentation 8 to 24 hours after TBI were enrolled into the "nontreatment" observation group and evaluated for infection and psychiatric symptoms, potential adverse effects of levetiracetam that are of particular concern. Computerized tomographic scans were used to determine the type and characteristics of injury, such as hemorrhage size, locus, and number.

TREATMENT

Levetiracetam 55 mg/kg/d was administered in 2 divided doses at 8 AM and 8 PM for 30 days, starting within 8 hours of injury. This dose was chosen to approximate the maximally effective antiepileptogenic dose (54 mg/kg/d) in animal kindling models[5] and because pharmacokinetic comparisons show similar areas under curve between rats and humans after an identical dose.[7] Levetiracetam was administered in tablet form or, for inpatients, in a solution, nasogastrically or intravenously, infused over 15 minutes. Children who were able to swallow but were unable to swallow tablets received the oral liquid formulation. All participants were hospitalized at the time of treatment initiation. Patients who were initially unable to swallow received levetiracetam intravenously or nasogastrically but changed to the oral liquid formulation when they were able to swallow. At discharge from hospital or rehabilitation, participants or their families and/or caregivers administered the medication, depending on the participant's degree of injury-related disability. Patient's compliance was assessed at each visit by pill count or liquid volume and by levetiracetam plasma trough (AM) level. Trough levels of less than 7 µg/mL were assumed to indicate noncompliance after reduced gastrointestinal absorption or increased renal clearance was ruled out.

Both treated and untreated participants received phenytoin for 1 week after TBI as standard (adult) care for prevention of "early" (<7 days after TBI) posttraumatic seizures[8] starting at 20 mg/kg. There is no standard of care for children, who received fosphenytoin sodium unless phenytoin was contraindicated. Phenytoin or fosphenytoin were initially administered intravenously at 20 mg/kg within 24 hours of injury. Serum levels of phenytoin were measured on treatment days 1, 2, 3, 4, and 7. Phenytoin dosages were adjusted daily on treatment days 1 to 4 to maintain levels in the 12- to 20-µg/mL range.

EVALUATIONS

Levetiracetam-treated participants were evaluated on days 3, 7, 14, 30, and 60 (1 month after treatment) in face-to-face visits to determine adverse events, infections, concurrent illnesses, and medication compliance. Adverse events were graded by the participants or caregivers on a scale of 0 to 3 (absent, mild, moderate, and severe, respectively) and temporally as once, intermittent, or constant. Infections were assessed with a structured questionnaire. A serious infection was defined as any antibiotic-treated infection.

Mood and behavior were evaluated on days 14, 30, and 60 using 2 validated adult and pediatric behavioral checklists, the Achenbach System of Empirically Based Assessment and the Center for Epidemiologic Studies Depression Scale.

Blood samples were obtained to determine the morning trough levels of levetiracetam on days 2, 3, 4, 7, 14, and 30, and the phenytoin levels on days 2, 3, 4, and 7. The trough levels were analyzed using high-performance liquid chromatography-electrospray tandem mass spectrometry. Complete blood cell count, electrolyte levels, and renal and liver functions were checked on days 1, 14, and 30.

Participants in the observational group were evaluated on days 14, 30, and 60 and were administered the infection and mood questionnaires. Both treated and untreated participants were administered a structured seizure questionnaire, developed by 2 epileptologist-investigators (P.K. and P.L.P.), at all the visits described and by telephone at 6, 9, 12, 15, 18, and 24 months after injury. Posttraumatic epilepsy was defined as a single unprovoked seizure occurring more than 7 days after injury.[4] Seizures were classified using International League Against Epilepsy criteria.[9]

STATISTICAL METHODS

Contingency table analysis was used to describe the demographic and clinical characteristics of the treated and un-

Table 1. Demographic and Clinical Characteristics of Participants Enrolled in Phase 2 Study of Treatment With Levetiracetam for Prevention of Posttraumatic Epilepsy

Characteristic	No. (%)			*P* Value
	Total	Treated With Levetiracetam	Not Treated With Levetiracetam	
Total	126 (100.0)	66 (100.0)	60 (100.0)	
Male sex	99 (78.6)	50 (75.8)	49 (81.7)	.42
Race				
White	53 (42.1)	29 (43.9)	24 (40.0)	.85
Black	66 (52.4)	33 (50.0)	33 (55.0)	
Other	7 (5.6)	4 (6.1)	3 (5.0)	
Ethnicity				
Hispanic	16 (12.7)	10 (15.2)	6 (10.0)	.39
Other	110 (87.3)	56 (84.8)	54 (90.0)	
Age, y				
6-12	26 (20.6)	15 (22.7)	11 (18.3)	.31
13-17	15 (11.9)	5 (7.6)	10 (16.7)	
18-39	42 (33.3)	24 (36.4)	18 (30.0)	
40-59	22 (17.5)	10 (15.2)	12 (20.0)	
60-69	9 (7.1)	7 (10.6)	2 (3.3)	
≥70	12 (9.5)	5 (7.6)	7 (11.7)	
Glasgow Coma Scale score[a]				
6-8	24 (19.0)	18 (27.3)	6 (10.0)	.03
9-11	10 (7.9)	6 (9.1)	4 (6.7)	
12-15	92 (73.0)	42 (63.6)	50 (83.3)	
Head injury (intracranial hemorrhage)				
Yes	114 (90.5)	59 (89.4)	55 (91.7)	.66
No	12 (9.5)	7 (10.6)	5 (8.3)	
Penetrating head injury				
Yes	5 (4.0)	4 (6.1)	1 (1.7)	.37
No	121 (96.0)	62 (93.9)	59 (98.3)	
Skull fracture				
Yes	32 (25.4)	18 (27.3)	14 (23.3)	.61
No	94 (74.6)	48 (72.7)	46 (76.7)	
Cranial surgery				
Yes	25 (19.8)	12 (18.2)	13 (21.7)	.72
No	97 (77.0)	51 (77.3)	46 (76.7)	
Unknown	4 (3.2)	3 (4.5)	1 (1.7)	

[a] Exclusion criteria were a Glasgow Coma Scale score of less than 6, based on the best score within 4 hours after a traumatic brain injury, to avoid high mortality.

treated participants and to identify factors that differed between these groups of participants and that would need to be controlled in groupwise comparisons. Crude and confounder-controlled estimates of the risk or mean level of study outcomes were compared between study groups using statistical modeling. All analyses were conducted using STATA version 11 (StataCorp). We implemented linear longitudinal models via xtreg to compare the time-averaged mean Achenbach System of Empirically Based Assessment and Center for Epidemiologic Studies Depression Scale scores. We used both the Kaplan-Meier method for crude analyses and Cox proportional hazards regression models for adjusted analyses to evaluate the risk of infection, mortality, and PTE over time. In PTE time-to-event analysis, death was considered as a competing risk using the procedure sterreg in STATA.

RESULTS

SCREENING, ENROLLMENT, AND FOLLOW-UP

Of the 422 participants screened, 205 (48.6%) were eligible, and 126 were enrolled: 86 adults and 40 children; 66 into levetiracetam-treated group (46 adults and 20 children) and 60 into the "untreated" observation group (40 adults and 20 children) (eFigures 1 and 2, http://www.archneurol.com).

DEMOGRAPHICS

Treated and untreated participants were similar with regard to sex and race/ethnicity. The levetiracetam-treated group included more younger children and more severely injured patients with Glasgow Coma Scale scores of 6 to 8 (19 of 66 treated participants vs 6 of 60 untreated participants; $P = .01$). Therefore, age and Glasgow Coma Scale score were adjusted in comparisons between treated and untreated groups (**Table 1**).

INJURY TYPE

Of the 126 participants, 114 (90.5%) had an intracranial hemorrhage as an inclusion criterion: 5 (4.0%) had penetrating head injury, 29 (25.4%) had a skull fracture, and 19 (15.1%) had an early seizure. Thirty-three participants (26.2%) had more than 1 injury type (eg, intracranial hemorrhage and skull fracture), including 22

Table 2. Potential Adverse Events in Levetiracetam-Treated Participants Ranked by Symptom Severity[a]

	Participants Affected, % (n = 126)		
Symptoms	Mild	Moderate	Severe
Headache	18	32	12
Fatigue	32	39	6
Drowsiness/somnolence	20	26	5
Memory impairment	30	11	5
Amnesia	29	8	5
Pain	24	20	5
Irritability	30	12	3
Dizziness	26	12	3
Anorexia	21	6	3
Emotional lability	15	8	3
Insomnia	11	5	5
Cognitive changes	12	11	3
Ataxia	24	7	2
Depression	23	12	0
Hostility	8	3	2
Vertigo	12	0	2
Nausea	26	3	0
Cough	32	3	0
Nervousness	11	0	0
Paraesthesia	6	5	0
Weight gain	8	0	0
Other	12	3	0

[a] Only symptoms experienced as severe (by any participant), moderately severe, or mild by 10% or more of participants in either adult or pediatric group are included.

of 66 treated participants (33.3%) and 15 of 60 untreated participants (25.0%).

DISPOSITION OF PARTICIPANTS

At 2 Months (Safety)

At 2 months, 118 of the 126 participants (93.7%) were followed up to study completion or death. Of the 66 treated participants, 8 (12.1%) stopped treatment early (7 of 46 adults [15.2%] and 1 of 20 children [5.0%]), of whom 6 were followed up to study completion (eFigures 1 and 2).

At 2 Years (Efficacy)

At 2 years, 100 of the 126 participants (79.4%) were followed up to study completion or death. Eight participants died, all adults (8 of 86 adult participants [9.3%]): 5 of 46 treated adults (10.9%) and 3 of 40 untreated adults (7.5%). Six of the 8 participants who stopped treatment early completed the 2-year follow-up; 20.6% subjects were lost to follow-up: 20.9% of adults and 20% of children.

SAFETY AND TOLERABILITY

There were no medication-related deaths or severe adverse events. Of the 8 treated participants who discontinued levetiracetam early (7 of 46 adults [15.2%] and 1 of 20 children [5.0%]), 2 (3%, both adults) did so for levetiracetam-related toxicity (somnolence, fatigue, irritability, and headache), and 6 (9%) for medication-unrelated reasons.

Table 3. Data on Trough Levels of Levetiracetam in Plasma by Treatment Day

Treatment Day	Mean Trough Level (95% CI), µg/mL
2	20.2 (16.2-24.2)
3	24.4 (19.1-26.6)
4	21.0 (16.3-25.7)
7	19.6 (15.0-24.2)
14	22.0 (17.5-26.5)
30	26.7 (21.9-31.5)

ADVERSE EVENTS

The most common symptoms were fatigue, headache, somnolence, memory impairment, pain, irritability, and dizziness. Severe symptoms were uncommon. Thirty-five percent of participants experienced depression (23% mild and 12% moderate). Depression was more common among adults (40%) than children (20%) ($P = .01$). There was 1 adult with transient suicidal ideation. One child (no adults) experienced psychosis, a transient mild paranoia with spontaneous resolution without levetiracetam discontinuation. Symptom severity did not correlate with trough levels for any group of related symptoms, except for depression in those older than 65 years (**Table 2**). There were no differences in rates of antibiotic-treated infections or in behavior and mood scores between treated and untreated participants (eTable).

SAFETY LABORATORY TESTS

The results from safety laboratory tests showed no patterns of abnormalities in complete blood cell count or chemistry profile. There was 1 instance each of low white blood cell count (2.2/µL on day 30 [to convert to $\times 10^9$ per liter, multiply by 0.001]) and thrombocytopenia (platelet count of 86 000 $\times$ 10^9/µL on day 14 [to convert to $\times 10^9$ per liter, multiply by 1.0]), both without clinical correlates.

TROUGH LEVELS

The mean trough levels of levetiracetam in plasma on days 2, 3, 4, 7, 14, and 30 ranged from 19.6 to 26.7 µg/mL, with no statistically significant difference between different treatment days. Comparisons of different routes of drug administration showed that C_{max} tended to be higher in participants who received levetiracetam intravenously (78.4 µg/mL) than in participants who received levetiracetam in tablet form (59.0 µg/mL) or nasogastrically (48.2 µg/mL) on day 3 ($P = .07$). There was no statistically significant difference in the area under curve (ie, the total exposure of the participant, as measured by levels of levetiracetam in plasma, to the drug over time) among participants who received levetiracetam orally (429.7 µg/mL/h), intravenously (377.3 µg/mL/h), or nasogastrically (341 µg/mL/h) ($P = .52$) (**Table 3**).

COMPLIANCE

Of the 46 treated adults, 7 (15.2%) had at least 1 trough level of less than 7 μm/mL; thus, 39 treated adults (84.8%) were 100% compliant. Of the 20 treated children, 8 (40.0%) had at least 1 trough level of less than 7 μm/mL; thus, 12 treated children (60.0%) were 100% compliant.

PTE/SEIZURES

Thirteen of 86 adults (15.1%) and 1 of 40 children (2.5%) developed PTE. Overall, 6 of 66 treated participants (9.1%) (5 adults and 1 child) and 8 of 60 untreated participants (13.3%) developed PTE (all adults) (relative risk, 0.57; $P = .27$). Among adults, 5 of 46 treated participants (10.9%) and 8 of 40 untreated participants (20.0%) developed PTE (relative risk, 0.47; $P = .18$). Of the 14 participants who developed PTE, 9 had complex partial seizures, and 5 had simple or complex partial seizures that were secondarily generalized (**Figure**; **Table 4**).

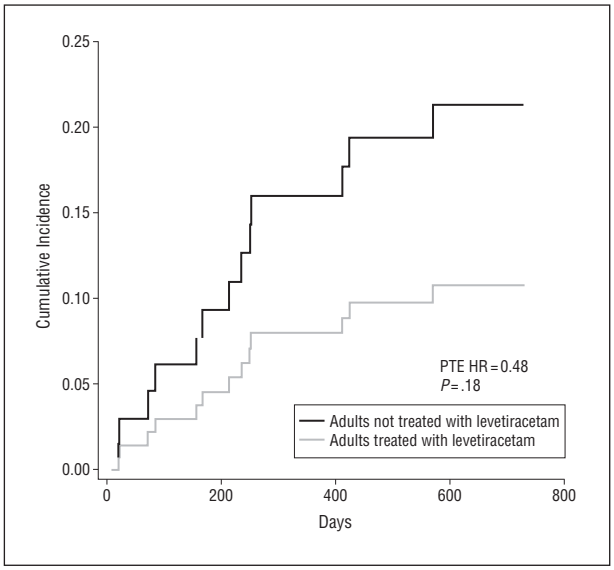

Figure. Cumulative incidence of posttraumatic epilepsy (PTE) between adults who were treated with levetiracetam and adults who were not treated, using Cox proportional hazards regression models, considering death as a competing risk, and including covariables to control for differences in age and injury severity. The PTE hazard ratio (HR) between these 2 groups of adults is 0.48 ($P = .18$).

COMMENT

There have been repeated attempts at prevention of PTE in the past, mainly with AEDs, all unsuccessful. There are reasons for these failed attempts at prevention: all AEDs evaluated to date have either had no antiepileptogenic effect in animals (phenytoin and carbamazepine) or had it at doses too high for human use (valproate sodium, phenobarbital, and clonazepam).[3,4] Unlike previously tested AEDs, levetiracetam has an antiepileptogenic effect in animals in clinically applicable doses with clinically relevant blood levels.[5]

The 55 mg/kg/d dose was selected because 54 mg/kg/d was the most effective dose in the kindling studies in which the antiepileptogenic effect of levetiracetam has been most studied.[5] In the kindling model, plasma levetiracetam levels were 10 to 25 μg/mL with a dose of 54 mg/kg/d.[5] In the pilocarpine–status epilepticus model, an increase in neuronal excitability and synchronization was blocked with levetiracetam levels of 12.7 to 55.2 μg/mL.[5] Our mean trough levels exceeded the lower end, and mean C_{max} levels on days 3 and 30 (59 μg/mL for both; P.K., unpublished data, 2012) exceeded the upper end of this range. These levels were attained quickly and were sustained: the mean trough levels on days 2 and 30 were 20.2 and 26.7 μg/mL, respectively.

The dose of 55 mg/kg/d is higher than the maximum adult recommended dose of 3000 mg/d but lower than the 60 mg/kg/d dose used in children.[6] It was started without titration in order to achieve the putative antiepileptogenic dose within 8 hours of injury. This was feasible because all the participants were inpatients at the time of treatment initiation. In adult patients with epilepsy whose dose of levetiracetam was titrated gradually to 1000 to 3000 mg/d, the most common adverse events are somnolence (15%), fatigue (15%), minor infections (13%), and dizziness (9%), with discontinuation rates of 4.4%, 1.3%, and 1.4%, respectively.[10] Similar adverse effects and rates are seen in children whose dose is titrated up to 60 mg/kg/d.[11] Psychiatric adverse events affect up to 13.3% levetiracetam-treated patients and lead to study withdrawal in 0.4% to 3% patients.[12] In the present study, full-dose initiation without titration was well tolerated.

Of the 66 treated participants, only 2 (3%) stopped the medication because of adverse events. The adverse events that these participants experienced were similar to those seen after TBI. Although the causation of these adverse events could not be determined in this open-

Table 4. Assessment of Mortality and Posttraumatic Epilepsy in Levetiracetam-Treated Participants and in Untreated Participants at 2 Years After Injury

Characteristic	No. (%)		Relative Risk		Adjusted *P* Value
	Treated	Untreated	Unadjusted	Adjusted	
All participants (n = 126)	66 (100.0)	60 (100.0)			
Posttraumatic epilepsy	6 (9.1)	8 (13.3)	0.70	0.47	.20
Mortality through 2 y	5 (7.6)	3 (5.0)	1.55	0.95	.95
Adults (n = 86)	46 (100.0)	40 (100.0)			
Posttraumatic epilepsy	5 (10.9)	8 (20.0)	0.54	0.45	.17
Mortality through 2 y	5 (10.9)	3 (7.5)	1.46	0.96	.96

label study, the severity of these adverse events did not generally correlate with plasma levetiracetam levels, suggesting that levetiracetam was not a critical factor.

Levetiracetam-treated adults had a 53% reduction in the risk of PTE. The results were not statistically significant because the present study was not powered for efficacy. Our study was designed and powered to evaluate safety, not efficacy. It was an open-label and nonrandomized study. The 2 adult groups differed in severity of injury and rate of loss to follow-up (both higher in the untreated adults). The number of participants was small. In the past, small open-label studies of PTE prevention with phenobarbital and phenytoin were positive, only to be followed by negative class 1 studies. It is also possible that levetiracetam could only delay the onset of epilepsy rather than prevent it. A longer follow-up may be needed to capture more PTE cases.

In our study, the pediatric PTE rate was low. To our knowledge, this was the first pediatric study to prospectively evaluate PTE in children for more than 18 months after TBI. We used the same inclusion criteria for children and adults. It is generally assumed that PTE risk factors are the same for both. There are few studies of PTE predictive factors in children.[2] These studies are small, often heterogeneous, including infants together with older children, and combining early and late seizures as "PTE" outcome. Our study suggests that either PTE may be less common in children than in adults or it may have different risk factors or a different time course.

In summary, this pilot study shows that treatment of patients with TBI who are at risk for PTE with 55 mg/kg/d levetiracetam, a dose that is antiepileptogenic in animals, is safe and well tolerated. Levetiracetam levels comparable to those effective in animal studies are achieved rapidly and maintained chronically. The findings support further evaluation of levetiracetam treatment for prevention of PTE in a phase 3 study.

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